

*January 2013*

## NIEHS Spotlight



### [Birnbaum gives keynote at environmental health meeting in India](#) Video

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### [Resnick elected AAAS Fellow](#) Audio

The American Association for the Advancement of Science has announced the election of lead researcher Michael Resnick, Ph.D., as a new fellow.



### [Suk honored for leadership by Society of Toxicology](#)

The Society of Toxicology has selected NIEHS Superfund Research Program Director Bill Suk, Ph.D., to receive its 2013 Founders Award.



### [Grassroots well water testing initiative reveals high levels of arsenic and radon](#) Video

A recent push to test well water revealed high levels of arsenic and radon in homes throughout the Tufonboro, N.H., community.



### [ASU appoints Halden to lead new Center for Environmental Security](#)

Superfund grantee Rolf Halden, Ph.D., is the new director of the Center for Environmental Security at Arizona State University.

## Science Notebook



### [2012 papers of the year](#)

From the nearly 2,500 NIEHS-funded studies published in 2012, leaders of the Institute's three research divisions selected 30 for special recognition as Papers of the Year.



### [NTP board gives go ahead for PAH research and systematic review](#)

The Board of Scientific Counselors endorsed the NTP multi-year PAH research concept with some minor tweaks, and accepted a working group report on systematic review.



### [Environmental health atlas provides interactive portal to promote awareness](#) Video

Longtime grantee Bruce Lanphear, MD., gave an audience at NIEHS a sneak peek at the Canadian Environmental Health Atlas website he and his colleagues are developing.



### [Climate impacts of kerosene lamps used in developing countries](#)

A new study, funded in part by NIEHS, suggests that replacing kerosene lamps with more efficient sources of artificial light would have a major impact in slowing the earth's warming trend.

## NIEHS Spotlight



### [NIEHS Partners gather in Friendship Heights](#)

The annual NIEHS Partners meeting Dec. 14 in Friendship Heights, Md., featured the lively discussion participants have come to expect in this casual roundtable venue.



### [Faculty position takes postdoc to remote Arctic community](#)

NIEHS postdoc Anshul Pandya, Ph.D., leaves this month for a tenure-track faculty position at the University of Alaska, Fairbanks Chukchi Campus.



### [Former NIEHS fellow pursues a career in mentoring postdocs](#)

As the new director of the Office of Postdoctoral Affairs at NCSU, Nisha Cavanaugh, Ph.D., is now in the best position to realize her ambition.



### [Environmental Polymorphisms Registry gets new leader](#)

The NIEHS Clinical Research Unit welcomed its newest member, Shepherd Schurman, M.D., to the fold as new director of the Environmental Polymorphisms Registry.



### [NIEHS employees recognized by NIH OD](#)

Ten NIEHS employees were among those recognized Dec. 19 at the 2012 NIH Office of the Director Honor Award ceremony in Bethesda, Md.



### [Stokes honored by U.S. Public Health Service](#)

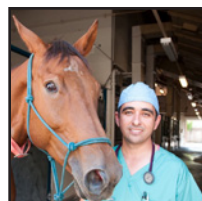
NTP center director Rear Adm. William Stokes, D.V.M., received the Distinguished Service Medal Dec. 19, during his flag officer retirement ceremony at NIEHS.

## Science Notebook



### [Papers explore chemical risk assessment in light of climate change](#)

The seven publications detail the ways climate change might affect how chemicals are transported and cause toxicity to ecosystems and humans.



### [Basic metabolism studies lead to a treatment for laminitis in horses](#)

A compound developed through NIEHS-funded Superfund research shows promise in treating a severe inflammatory disorder.



### [Uranium exposure linked to increased lupus rate](#)

People living near a former uranium ore processing facility in Ohio are experiencing a higher than average rate of lupus, according to a new NIEHS-funded study.



### [NICEATM holds workshop on new safety tests for pertussis vaccines](#)

NIEHS and FDA scientists joined other experts from around the world at a workshop on improved methods and approaches for safety testing of whooping cough vaccines.



### [Casey meets with international experts to assess endocrine disruptor testing](#)

NTP scientist Warren Casey, Ph.D., participated in expert meetings Nov. 28-30 about *in vitro* methods for detecting substances that might interfere with normal hormone function.

## Inside the Institute



### [NIEHS celebrates diversity and generosity on International Day](#)

NIEHS offered employees and contractors sustenance for the body and the soul during this year's International Day celebration Dec. 12.

## Calendar of Upcoming Events

- **Jan. 4**, in Rodbell C, 11:00 a.m.-12:00 p.m. — Laboratory of Reproductive and Developmental Toxicology Seminar Series presentation on “Regulation of Cytochrome P450 Enzyme Proteolysis by Reactive Nitrogen Species,” by Edward Morgan, Ph.D.
- **Jan. 8**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Distinguished Lecture Series featuring Noel Rose, M.D., Ph.D., speaking on “Myocarditis: An Environmentally Initiated Autoimmune Disease”
- **Jan. 9-11**, in Rodbell Auditorium, 8:30 a.m.-4:30 p.m. — Nano Exposure Workshop, followed by Nano Characterization Workshop
- **Jan. 10-11 (offsite event)**, at the Keck Center in Washington, D.C., and online — Emerging Science Workshop on Integrating Environmental Health Data to Advance Discovery, [register](#)
- **Jan. 16-17 (offsite event)**, at the California Environmental Protection Agency in Sacramento and online — [Cumulative Impacts and Children's Environmental Health](#)
- **Jan 17**, in Rodbell Auditorium, 10:00-11:00 a.m. — Office of the Director Seminar with Story Landis, Ph.D.
- **Jan. 23 (offsite event)**, at Louisiana State University in Baton Rouge and online — Superfund Research Program Symposium on Response, Recovery, and Resilience to Oil Spills and Environmental Disasters: Engaging Experts and Communities, [registration](#) required
- **Jan. 25**, in Rodbell Auditorium, 10:30-11:30 a.m. — Martin Luther King Jr. Observance by Griffin Rodgers, M.D.
- **Jan. 28-30**, in Rodbell Auditorium, 8:30 a.m.-4:30 p.m. — BPA Grantee Research and Women's Reproductive Health Meeting
- View More Events: [NIEHS Public Calendar](#)

## Science Notebook



### [This month in EHP](#) Audio

Environmental Health Perspectives goes paperless in January with its first entirely electronic issue featuring a cover article on cooler-by-design architecture and engineering.



### [Rose to give distinguished lecture](#) Video

The first 2013 NIEHS distinguished lecture, “Myocarditis: an environmentally initiated autoimmune disease,” will be presented Jan. 8 by Noel Rose, M.D., Ph.D.



### [Upcoming data integration workshop](#)

An innovative NIEHS-sponsored program continues its workshop series with an exploration of Integrating Environmental Health Data to Advance Discovery Jan. 10-11.

## Extramural Research

### [Extramural papers of the month](#)

- [Mechanism for melanoma risk in people with red hair and fair skin](#)
- [Early exposures to air pollution linked with autism](#)
- [Flame retardant Firemaster 550 confirmed as endocrine disruptor](#)
- [Prenatal mercury and ADHD](#)

## Intramural Research

### [Intramural papers of the month](#)

- [Chloride channel regulation may lead to improvements in vascular disease](#)
- [Mechanisms of anticancer drug resistance](#)
- [New insights into lung dendritic cell migration in adaptive immune responses](#)
- [Tobacco smoke exposure \*in utero\* increases adult cardiovascular disease risk](#)



# NIEHS Spotlight

## Birnbaum gives keynote at environmental health meeting in India

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., traveled to New Delhi, India, Dec. 6 to present the keynote address at an international symposium on occupational health. Organized by the [Centre for Occupational and Environmental Health \(COEH\)](#) at [Maulana Azad Medical College \(MAMC\)](#), the gathering of specialists Dec. 6-8 was titled “An International Meet on Climate, the Workplace, and the Lungs.”

The COEH is governed by the Indraprastha (Delhi) Society for Occupational and Environmental Health, a research and government advisory group dedicated to preventing work-related injury and ill health, as well as environmental illness, through education, training, clinical action, and monitoring regulatory compliance. A central goal of the COEH is developing the specialty of occupational and environmental medicine in India.

Birnbaum, the only U.S. federal scientist presenting at the meeting, joined environmental and occupational health experts from North America, Europe, India, and other Asian nations in a wide-ranging exploration of existing and emerging environmental health issues in India.

### Primer on environmental health focuses on India

Birnbaum set the tone for her talk on “NIEHS and the Future of Environmental Health” by describing what makes NIEHS stand out among its sister institutes and centers at NIH. “NIEHS is unique at the NIH, because we are the only one whose research has a primary focus on preventing disease, rather than diagnosing and treating it,” she told her audience. “This means that we have a commitment to conducting outreach, education, training, and supporting community partnerships, in addition to the highest quality, most rigorous laboratory-based science.”

She then moved into a broad discussion of environmental health research supported by NIEHS with special relevance to health concerns in India. These areas of research include persistent issues, such as arsenic in drinking water and indoor air pollution from cookstoves, and emerging problems related to development, such as obesity, air pollution, electronic waste, climate change, and asbestos.



*Birnbaum also discussed the new NIEHS strategic plan, which includes a statement of the Institute's strong commitment to global environmental public health. Her talk featured a number of references to the extensive research and preventive efforts NIEHS has funded in developing nations. (Photo courtesy of Steve McCaw)*



**Linked video:**  
[Watch an Australian Broadcasting Corporation report on asbestos in India \(03:10\)](#)

(Launches in new window)

Download Media Player:  Flash 



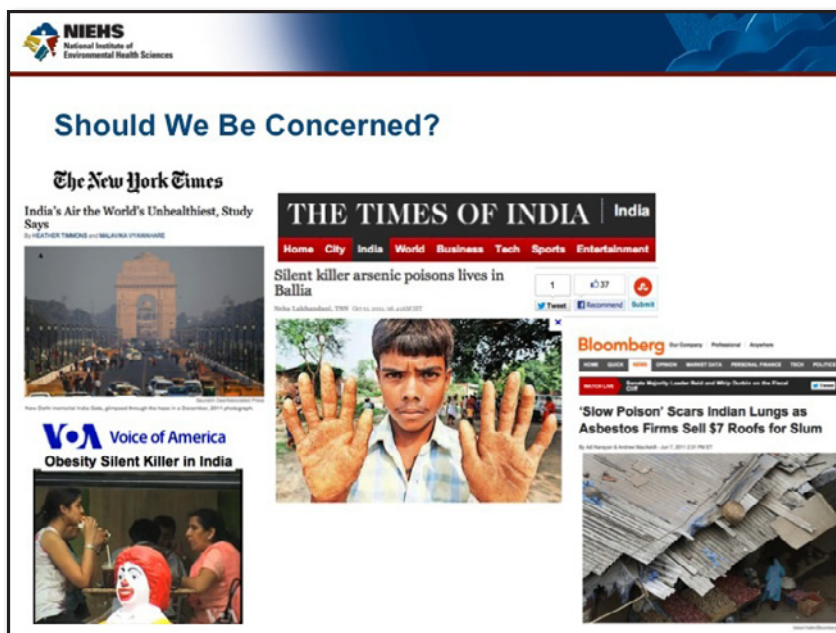
As Birnbaum noted throughout her presentation, NIEHS-supported research on problems that North Americans have confronted can help build the foundation for advancing awareness, research, and preventive efforts to promote occupational and environmental health in India and other developing nations. “The environmental health issues that we face in the U.S. are not unique to our country,” she explained. “India is suffering from some of the same environmental health effects that affect the U.S.”

### The world’s premier environmental health sciences research institution

Birnbaum’s keynote address in New Delhi is but the latest example of the emergence of NIEHS as a model for environmental health sciences research worldwide. Among its many such initiatives in the past two years alone, the Institute has partnered with other government agencies in the international Global Alliance for Clean Cookstoves; worked with the World Health Organization (WHO) and Pan American Health Organization to bring environmental health to the forefront of the international debate on climate change and economic development; spearheaded a symposium with the European Commission on low dose effects of endocrine disruptors; hosted a visit by representatives of the French health research organization Inserm; and played a major role at international dioxin symposia in Belgium and Australia.

Naturally enough, when T.K. Joshi, director of the Occupational and Environmental Health Programme at COEH, began putting together the conference program, he turned for American expertise to Birnbaum, as well as environmental lung disease expert [Arthur Frank, M.D., Ph.D.](#), of the Drexel University School of Public Health. They joined representatives of WHO, the Occupational Health Clinics for Ontario Workers, the United Nations Environment Programme, several Indian organizations and government agencies, and other specialists throughout the world.

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*Birnbaum let headlines tell part of the story, as she underscored the health issues that India and the U.S. both experience. (Slide courtesy of Linda Birnbaum)*

### Impacts of E-waste in India

- 4.7 tons of e-waste generated in India per year
- Lead, Mercury, Cadmium, PAH's, flame retardants
- Studies in China found:
  - High rate of adverse birth outcomes
  - Lower Apgar scores
  - Unsafe lead levels in cord blood

*With this slide as a backdrop, Birnbaum pointed to NIEHS-funded research drawing attention to, and documenting, the impact of exposure to mixed metals from unregulated recycling and disposal of electronic waste. (Slide courtesy of Linda Birnbaum)*

# Resnick elected AAAS Fellow

By Eddy Ball

In the Nov. 30, 2012 issue of Science, the American Association for the Advancement of Science (AAAS) announced the election of lead researcher Michael Resnick, Ph.D., as a new fellow. Resnick is head of the Chromosome Stability Group in the NIEHS Laboratory of Molecular Genetics.

The organization will present Resnick with a certificate and gold rosette Feb. 16 in Boston during the AAAS Fellows Forum, which is part of the 2013 AAAS annual meeting, honoring him for seminal contributions in understanding the molecular basis of DNA repair by homologous recombination.

“This is an honor Mike richly deserves,” said NIEHS/NTP Director Linda Birnbaum, Ph.D., when she learned of the award. “His work is an excellent example of the way basic research can broaden understanding of environmental health and inform clinical research, especially with his group’s cross-divisional collaboration with our Clinical Research Unit physicians on the role of the master regulator p53, an early responder to DNA damage, in inflammatory responses.”

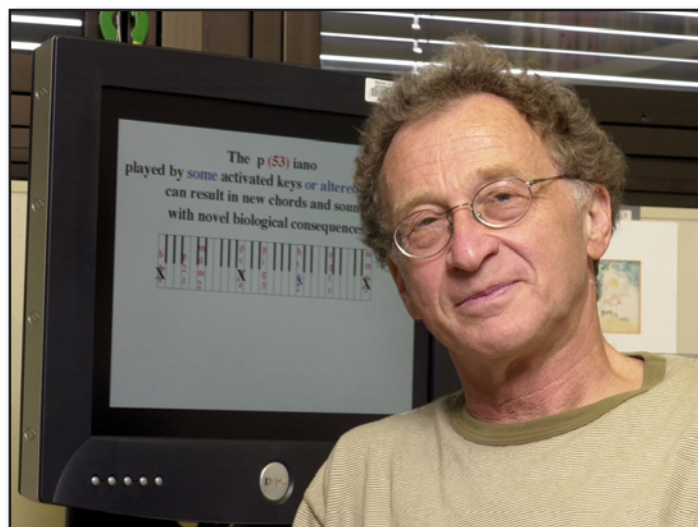
Resnick and his group are interested in genetic and structure-function relationships between repair, replication, mutation avoidance, and signaling responses; sources of DNA damage, especially double-strand breaks, mechanisms of repair, and genetic consequences; and environmental agents and conditions that impact genome stability. The findings are integrated into his studies on the organization and evolution of the human p53 tumor suppressor master regulatory network and consequences of cancer-associated mutations.

Resnick joined NIEHS in 1979 following postdoctoral fellowships with the Medical Research Council in London and Oak Ridge National Laboratory in Tennessee, and positions at the University of Rochester in New York and the MRC National Institute for Medical Research in London. He was the NIEHS Scientist of the Year in 2008. His group has been awarded three NIEHS Best Paper of the Year Awards and authored numerous Division of Intramural Research papers of the month.

## AAAS – 164 years of advancing scientific excellence

Founded in 1848, AAAS serves some 262 affiliated societies and academies of science, representing more than 10 million individuals. The AAAS journal Science has the largest paid circulation of any peer-reviewed general science journal in the world, with an estimated total readership of one million.

AAAS began electing fellows in 1874, an honor bestowed upon members by their peers. Fellow nominations may be made by the steering groups of the association’s 24 sections, by the chief executive officer, or by any three fellows who are current AAAS members, so long as two of the three sponsors are not affiliated with the nominee’s institution. Each nominee must receive the approval of a majority of the steering group members.



Newly elected AAAS fellow Mike Resnick holds seven patents for research conducted in his lab and has published more than 160 peer-reviewed studies indexed by PubMed. (Photo courtesy of Steve McCaw)



[Listen as Resnick discusses his research into p53 and the innate immune system \(03:15\)](#)

[Read Transcript](#)

## In good company

Resnick joins a select group of NIEHS scientists elected as AAAS fellows in previous years:

- Joel Abramowitz, Ph.D., special assistant to the scientific director
- Marian Johnson-Thompson, Ph.D., former director of Education and Biomedical Research Development
- James Mason, Ph.D., researcher in the Drosophila Chromosome Structure Group in the Laboratory of Molecular Genetics
- James Putney, Ph.D. head of the Calcium Regulation Group in the Laboratory of Signal Transduction
- Anne Sassaman, Ph.D., director emeritus of the Division of Extramural Research and Training
- Barbara Shane, Ph.D., former NTP staff scientist and executive secretary of the NTP Board of Scientific Counselors
- Samuel Wilson, M.D., head of the DNA Repair and Nucleic Acid Enzymology Group in the Laboratory of Structural Biology
- Jerrel Yakel, Ph.D., head of the Ion Channel Physiology Group in the Laboratory of Neurobiology

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## Suk honored for leadership by Society of Toxicology

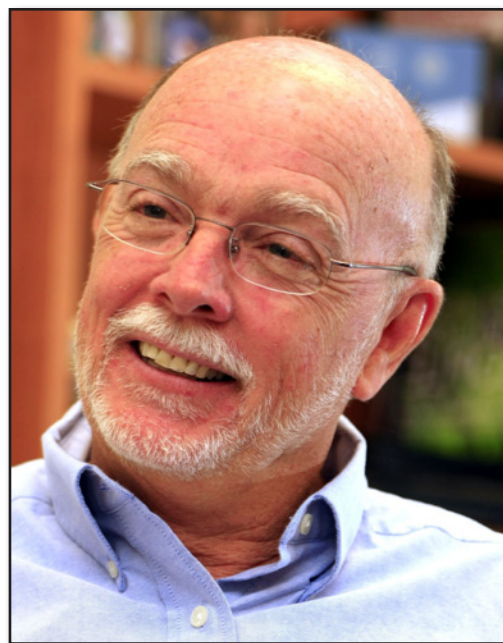
*By Eddy Ball*

The Society of Toxicology (SOT) has selected NIEHS Superfund Research Program (SRP) Director Bill Suk, Ph.D., to receive its 2013 [Founders Award](#). SOT will present Suk with a plaque and a stipend at a ceremony March 10 during its [52nd annual meeting](#) in San Antonio.

In her announcement of Suk's award, SOT Awards Committee Chair Mary Ann Smith, Ph.D., described the award as a well-deserved honor. "The Founders Award is awarded to a full member of the society who has demonstrated outstanding leadership in fostering the role of toxicological sciences in safety decision-making, through development and/or application of state-of-the-art approaches that elucidate, with a high degree of confidence, the distinctions for humans between safe and unsafe levels of exposures to chemical and physical agents," she wrote.

### Superfund's 25 years of leadership in toxicology

Suk has served as SRP director since the program's inception in 1987. He has led the development of comprehensive research, remediation, education, translation, and outreach efforts, to prevent



2013 Founders Award winner Suk (Photo courtesy of Steve McCaw)



disease and illness related to exposure to toxic substances generated at the more than 15,000 federally managed hazardous waste sites in the U.S. The program has nurtured productive relationships with the U.S. Environmental Protection Agency, which oversees hazardous waste cleanup at Superfund sites, and the Agency for Toxic Substances and Disease Registry, which shares the SRP public health mission.

In recognition of its milestone anniversary, SRP produced a [commemorative booklet](#) on its accomplishments in the U.S. and abroad for its annual meeting Oct. 22-24, 2012 in Raleigh, N.C. ([see story](#)). At the meeting, grantees, trainees, and friends of the program looked ahead to the future directions of SRP as a model for global health interventions in developing countries where at least 20 percent of deaths are directly attributable to preventable environmental exposures.

### **Honoring a pioneer in applying toxicology to public health**

Suk received his Ph.D. in microbiology from the George Washington University and his Masters in Public Health in health policy from the University of North Carolina at Chapel Hill. He has also been a National Science Foundation fellow.

Affiliated with a number of organizations and committees concerned with toxic exposures and public health, Suk is a member of the Roundtable on Environmental Health Sciences, Research, and Medicine at the Institute of Medicine of the National Academies; International Advisory Board of the Chulabhorn Research Institute in Bangkok; and World Health Organization Consultation on Scientific Principles and Methodologies for Assessing Health Risks in Children Associated with Chemical Exposures. He also serves on a number of trans-NIH committees.

He is a member of the editorial boards of a number of international journals, including Environmental Health, Toxicological and Environmental Chemistry, International Journal of Occupational Medicine and Environmental Health, and the Central European Journal of Public Health.

In addition to his recognition by SOT, Suk has received NIH honors for his many efforts, as well as the U.S. Department of Health and Human Services Secretary's Award for Distinguished Service. He is a recipient of the Roy E. Albert Memorial Award for Translational Research in Environmental Health from the University of Cincinnati; the Child Health Advocate Award from the Children's Environmental Health Network; the John P. Wyatt Lecture Award in Environmental Health and Disease from the University of Kentucky; and the Adel F. Sarofim Award for Excellence in Combustion Research. He is a fellow of the Collegium Ramazzini.

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## **Grassroots well water testing initiative reveals high levels of arsenic and radon**

*By Sara Mishamandani*

A recent push to test well water revealed high levels of arsenic and radon in homes throughout the Tuftonboro, N.H., community. Following a presentation in June 2012 by the Dartmouth College Superfund Research Program (SRP) Community Engagement Core (CEC) to the Town of Tuftonboro Board of Selectmen about the importance of regular well testing, the [Tuftonboro Conservation Commission \(TCC\)](#) led an effort to increase well testing rates in the region.

**In Small Doses:**



**Arsenic**



**Linked video:**

[Watch the Dartmouth SRP video, which reaches out to the general public to encourage testing private wells for arsenic contamination \(10:00\)](#)

(Launches in new window)

Download Media Player:  Flash 

In New Hampshire, one in every five wells has more than 10 parts per billion of arsenic, which is above the U.S. Environmental Protection Agency standard for safety. [A new report](#) released Dec. 4, 2012, by the U.S. Geological Survey (USGS) shows that low levels of arsenic in drinking water is much more widespread. The researchers found that nearly 40 percent of New Hampshire's groundwater likely contains at least low levels of naturally occurring arsenic.

### The well testing initiative in Tuftonboro

In partnership with the Dartmouth CEC and the N.H. Department of Environmental Services (DES), the commission made it easier for residents to test their water, by providing a drop-off location and then delivering samples to the state lab. To publicize the well water testing opportunity, they wrote articles for the town newsletter and local newspapers, and placed notices in the town post offices, with information about the health risks associated with elements commonly found in N.H. wells.

After testing, results were sent directly to the residents. In October 2012, the Dartmouth CEC presented the collective results, which showed that 34 percent of samples exceeded the U.S. Environmental Protection Agency's maximum contaminant level for arsenic, and 25 percent of the samples were above the advisory level for radon.

Due to these high levels, DES hosted a forum Nov. 13 to allow residents to ask questions about their test results and remediation options. The Dartmouth CEC continues to work with the residents in the community, informing them of the importance of regular well testing and providing them with options to reduce exposure to arsenic and radon from well water.

"Most local residents aren't informed about the health effects and the need to test for arsenic when their water is tested," said Steve Wingate, a member of the TCC and a local resident. "Dartmouth has helped us with technical information, and can 'talk the talk' where we struggle with informing residents."



*Steve Wingate, left, and Nancy Piper, of the TCC, worked with Dartmouth SRP to raise awareness of the need for well testing. (Photo courtesy of Steve Wingate)*



*Christine Bowman, right, a DES employee who works in the Municipal Water group, helped a homeowner understand options for reducing exposure, at the well water forum in November 2012. (Photo courtesy of Steve Wingate)*

## Reaching out to others

Dartmouth SRP researcher Bruce Stanton, Ph.D., was featured in a [public radio report](#) after the new study from the USGS was published. Stanton explained that these levels could be affecting people's health.

"Some preliminary studies show that these very low arsenic exposures could be making people more susceptible to lung infections," said Stanton. "The bottom line is there's not a lot of research at these low levels, we're beginning to do research, and we are finding significant effects."

In the radio report, Stanton added that the safest thing to do, for people concerned about water quality, is to get their wells tested.

Dartmouth SRP has created a ten-minute video about the risks associated with exposure to potentially harmful amounts of arsenic in private well water. The video includes information about how arsenic moves into groundwater, how it is detected, and what can be done to remove it.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program, Worker Education and Training Program, and Division of Extramural Research and Training.)

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## ASU appoints Halden to lead new Center for Environmental Security

*By Sara Mishamandani*

Rolf Halden, Ph.D., an Arizona State University (ASU) environmental engineering professor and NIEHS Superfund Research Program (SRP) grantee, is the new director of the [Center for Environmental Security \(CES\)](#) at ASU, an innovative initiative to manage environmental stress to protect human health and critical ecosystems.

[Halden](#) sees CES as a way to address the need to work on a regional, national, and global scale to protect environmental quality and human health, using both traditional and innovative public health strategies.

"The goal of CES is to protect human populations and our planet by detecting, minimizing, and ultimately eliminating harmful chemical and biological agents through engineering interventions," said Halden. "We will be utilizing a proactive approach to examine chemical and biological threats in the environment locally and globally, to track human diseases of environmental etiology, and to develop intervention strategies suitable for mitigating these threats."



*In addition to leading CES, Halden formed In Situ Well Technologies, a spinout company that focuses on remediation for contaminated water resources and aquifers. (Photo courtesy of ASU)*



## Uniting public health engineering and global security

The center will be the first of 11 research centers at ASU's Biodesign Institute, which will partner to leverage expertise and resources from ASU's Security and Defense Systems Initiative (SDSI). By using environmental engineering to anticipate threats and prevent avoidable diseases, Halden's center will focus on national and global security, through a transdisciplinary approach, to help answer numerous present-day sustainability challenges and to offer a notable return on investment.

"Public health engineering saves lives and money," Halden explained. "More than half of humanity's health problems are dependent, either directly or indirectly, on environmental factors. People get exposed to potentially harmful agents through food, air, water, and soil. We are looking at all relevant exposure routes with the goal to intervene early."

The major research themes of CES include environmental monitoring as a means of threat detection; environmental epidemiology for health impact assessment; public health preparedness for bioterrorism prevention; innovative environmental diagnostics and management strategies using microcosm arrays and policy interventions; and food safety and security through microbial drug-resistance tracking.

The center was established in late 2012, with funding from the Piper Charitable Trust, as well as the ASU SDSI, Fulton Schools of Engineering, and Office of Knowledge Enterprise Development. CES also has support from the Department of Defense for two projects.

## A focus on Superfund research

Halden's past and current NIEHS-funded research concentrates on the development of an *in situ* microcosm array (ISMA) remedial design device and a sampling tool for assessing bioavailability and toxicity of sediments. Both projects address the pressing need of Superfund stakeholders to determine, in a convenient and reliable way, both human health risks from contaminated sediments and the effectiveness of implemented remediation strategies.

His team at the ASU Biodesign Institute recently reached an arrangement with Geosyntec Consultants, an international environmental remediation firm, to jointly develop the NIEHS-funded ISMA technology for commercialization.

Halden has received SRP funding since 2006, resulting in over 35 peer-reviewed publications, multiple patent applications, and three SRP Research Briefs ([169](#), [180](#), and [199](#)). Halden's research has also sparked two startup companies.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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## NIEHS Partners gather in Friendship Heights

*By Eddy Ball*

The annual NIEHS Partners meeting Dec. 14, 2012, in Friendship Heights, Md., featured the lively discussion participants have come to expect in this casual roundtable venue. Along with the welcome opportunity to talk personally with NIEHS/NTP Director Linda Birnbaum, Ph.D., this year's gathering also featured an informal symposium on One-NIEHS endocrine disruption research, by representatives of the Institute's three research divisions.

The purpose of these meetings with the [NIEHS Partners](#) is to seek input and improve communication with communities and organizations directly affected by the mission and research of NIEHS. The membership represents diverse groups, including disease, disability, and environmental education and advocacy organizations. The group lends grassroots perspectives to the research agenda of NIEHS, while serving as a key contributor to the translation of research findings to the public, policy makers, and private foundations.



*Partner Nsedu Obot Witherspoon, right, took advantage of the informal setting, to air concerns about the effects of environmental exposures on children's development. Witherspoon is a former NIEHS council member and the executive director of the Children's Environmental Health Network. (Photo courtesy of John Schelp)*

### **Research divisions collaborate on endocrine research**

Birnbaum, who obviously enjoys the camaraderie of the Partners, opened the meeting with a sincere expression of her appreciation of their input. "You all are a really terrific group," she told the 15 attendees, as participants prepared to introduce themselves and enjoy 2 1/2 hours of open discussion over lunch. The final two hours of the meeting were devoted to presentations by lead researcher Ken Korach, Ph.D., of the Division of Intramural Research; lead researcher Sue Fenton, Ph.D., of the Division of the National Toxicology Program; and health scientist Thaddeus Schug, Ph.D., of the Division of Extramural Research and Training.

Along with Birnbaum, whose interest in endocrine disruption, and the atypical dose-response patterns to hormone-like chemicals, has inspired several of her recent talks, Korach, Fenton, and Schug described the Institute's integrated research strategy to better understand the public health impact of exposure.



*Birnbaum, right, made a point that low-dose exposures to hormone-like chemicals, at certain stages of development, can potentially be very harmful. Schug, left, spoke about NIEHS grants for endocrine-disruption research. (Photo courtesy of John Schelp)*

As the speakers explained, endocrine-disrupting compounds can affect human health from preconception to old age, with especially significant impacts during developmental windows of susceptibility. Recent research suggests that exposures may have effects on gene expression that can manifest years and decades later, triggering a range of disease and dysfunction that may even affect offspring in subsequent generations.

### **Keeping a finger on the pulse of environmental health**

NIEHS reaches out to the Partners in several ways, including such gatherings as the informal meeting in Friendship Heights, monthly conference calls, collections of new NIEHS-supported scientific studies, and participation by representatives at meetings of the [National Advisory Environmental Health Sciences Council](#). Along with representatives of the research divisions, staff members from the NIEHS Bethesda, Md., office



*The Partners joined NIEHS representatives for a photo opportunity, at the conclusion of the program. (Photo courtesy of John Schelp)*

interact with the Partners. At this year's meeting, NIEHS Legislative Liaison Mary Gant and Special Advisor for Public Health John Balbus, M.D., were on hand to offer updates as well.

"We didn't have prepared speeches or PowerPoints. Just an open conversation around a big table," said Special Assistant for Community Engagement and Outreach John Schelp of the [Office of Science Education and Diversity](#), which organizes the events.

This kind of fluid agenda strikes a positive chord with the Partners. "Each year, the NIEHS shares advances in cutting edge research with the Partners, so we can help our public understand the role that environment may be playing in the disability or health condition each group represents," said Betty Mekdeci, Partners co-chair and director of Birth Defect Research for Children. "We are also privileged to be able to ask Dr. Birnbaum any question that will further our understanding of the science."

Partner co-chair Karen Miller, founder and president of the Huntington Breast Cancer Action Coalition, agreed and added her own appreciation of the Institute's cross-disciplinary approach to environmental health science. "NIEHS really brings everything together... dynamic... energizing... opposite of silos. This is the model to emulate, because every single thing is connected," she said.

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## **Faculty position takes postdoc to remote Arctic community**

*By Eddy Ball*

Fortunately for NIEHS postdoc Anshul Pandya, Ph.D., and his wife, the couple knows what to expect when they move to the sublime landscape of rural northwestern Alaska this month — bone-chilling winter cold with highs most days staying well below zero, followed by a brief, but glorious, Alaskan summer they believe is well worth the wait.

Pandya is a graduate of the University of Alaska Fairbanks (UAF), where he will return to assume a tenure-track faculty position at the [UAF Chukchi Campus](#) in the state's Northwest Arctic Borough. His wife lived in Nome



before they moved to the Triangle together. After Pandya completed his doctorate in 2009, and prior to joining NIEHS for his postdoctoral training later that summer, he was an adjunct professor in the [Rural Alaska Honors Institute \(RAHI\)](#), which served a minority population very similar to the people in the northwestern Inupiat hub where he'll be teaching and conducting research.

"It's like going home," Pandya said. "I'm really looking forward to moving out to Alaska, living in the wilderness, and being outdoors in the summers."

### Training at the bench and beyond

For the past 3 1/2 years, Pandya has worked in the Laboratory of Neurobiology [Ion Channel Physiology Group](#) headed by Jerrel Yakel, Ph.D. In his work with Yakel's group, Pandya brought his perspective, as a pharmacologist, to research that focused on the nicotinic acetylcholine receptor channels and their role in neurological disorders. He was first author of two papers on allosteric modulators of those receptors, and a co-author or contributor on several other papers from the group.

But a teacher/researcher is not merely a source of knowledge, as Pandya recognized early in his fellowship at NIEHS. So, Pandya soon began looking for additional mentors and career development opportunities.

In 2011, he began writing Division of Intramural Research paper of the month summaries, working with Science Editor Robin Arnette, Ph.D., as well as other articles for the Environmental Factor. Later that year, he jumped at the chance to work with the NIEHS [Office of Science Education and Diversity \(OSD\)](#),



*"I've had a good experience here," Pandya said of his time as a trainee. "I've enjoyed working at NIEHS, and Jerry [Yakel] gave me a lot of freedom to explore career development opportunities, as well as take higher-risk approaches to my research." (Photo courtesy of Steve McCaw)*

### Blending academics with community

In his new position, Pandya will be a part of the UAF educational outreach mission and live in a very small community of native Alaskans in the town of Kotzebue, which has about 4,000 residents and is home to the Chukchi Campus. He will probably teach a few courses at satellite locations in some of the ten smaller villages in the region, where some 3,000 more people live in the 38,000 square mile [NANA region](#), which was named for its precursor, the Northwest Alaska Native Association, and is roughly the size of Indiana.

Because of the vastness, remoteness, and susceptibility to permafrost freezing and melting, the NANA region does not have highway access to its villages. When UAF Chukchi Campus faculty members commute, they fly in and out in small aircraft. Barges deliver heating oil when the Chukchi Sea of the Arctic Ocean is navigable.

As highly trained scientists who live where they work, Pandya and his UAF colleagues serve as role models for young people. They are also an integral part of a close-knit community where people often depend on others. "People who can fly into larger towns and cities often bring back supplies to help others through the winters," he said. "People are really friendly there, and the feeling is that cooperation [rather than competition] brings you a better future."

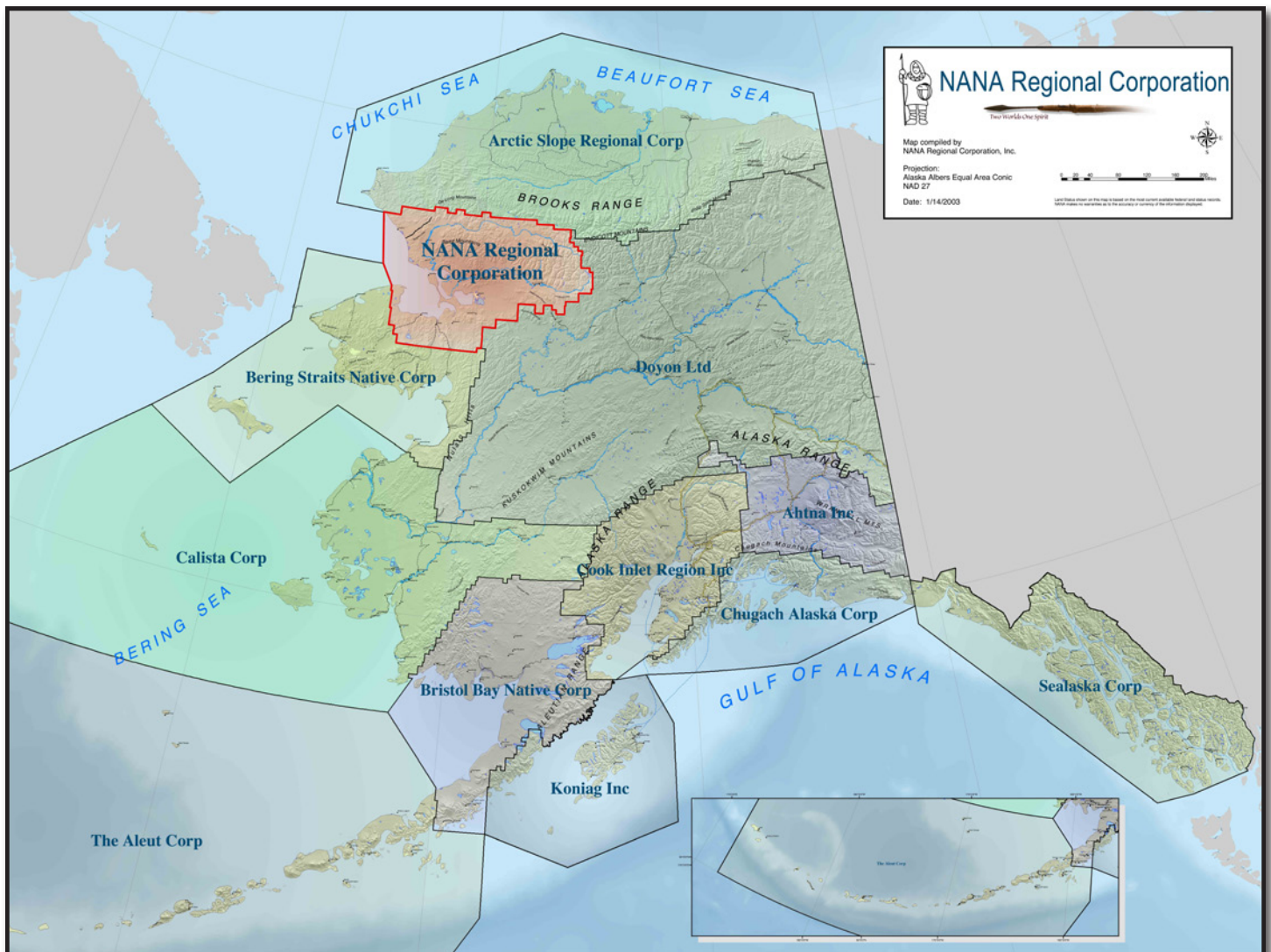
headed by Ericka Reid, Ph.D., inspired in part by his early experiences as part of RAHI. He also served as a mentor for NIH Summer Intern Program participants in his lab group.

These off-bench training experiences proved to be helpful in landing his new job at UAF, where he will be teaching and mentoring native Alaskan freshman and sophomore students in life science courses. Writing about science outside his field gave him experience in communicating a range of topics to a more general audience.

Attending the annual conferences of the Society for Advancement of Chicanos and Native Americans in Science and the Annual Biomedical Research Conference for Minority Students in 2011 and 2012 as a representative of OSED, Pandya had an opportunity to network, as well as learn how to explain NIEHS and NIH training and employment opportunities to young scientists from underrepresented populations.

Pandya also took advantage of opportunities to learn from outside speakers he hosted at NIEHS. “We talked about what I should do when I transition my career from a postdoc, what precautions to take, how to negotiate a package, and what to look out for during my job search,” he said.

That combination, plus proactive efforts to establish personal contact with search committee members at the institutions where he applied, led to four interviews during Pandya’s six-month search for the right position.



*Shown in red, the sparsely populated NANA region borders the Arctic Slope, not far from Russia. (Map courtesy of the NANA Corporation)*



# Former NIEHS fellow pursues a career in mentoring postdocs

By Sheila Yong

During her time as a postdoctoral fellow at NIEHS, Nisha Cavanaugh, Ph.D., discovered her passion in advocating for postdoctoral fellows and helping them seek out the best opportunities available to them. Equipped with her previous leadership experience as the chair of the NIEHS Trainees Assembly (NTA), she wanted to continue her quest to assist postdoctoral fellows in exploring potential career paths and help them acquire the skills they need to achieve their goals.

As the new director of the [Office of Postdoctoral Affairs \(OPA\)](#) at North Carolina State University (NCSU), a position she assumed in December 2012, Cavanaugh is now in the best position to realize her ambition.

## Preparing for a career away from the bench

While serving as the NTA chair in 2010-2011, Cavanaugh worked closely with Diane Klotz, Ph.D., the former director of the Office of Fellows' Career Development (OFCD). Using her own career experience as an example, Klotz was instrumental in advising Cavanaugh regarding careers away from the bench.

"My postdoctoral experience at NIEHS and my interaction with Dr. Klotz allowed me to better understand the various challenges postdoctoral fellows often face both in and outside the lab, and it put me in a position to help future postdocs overcome these challenges," Cavanaugh commented. She believes that these qualities will enable her to carry out her duties more effectively as the OPA director. Her responsibilities at OPA include overseeing the development of programs and services for postdoctoral scholars that will enhance their experience at NCSU, facilitating networking opportunities for them in the Research Triangle Park area, and creating a network among past and present NCSU postdocs.

Cavanaugh is also grateful to her former supervisor, Samuel Wilson, M.D., who heads the [DNA Repair and Nucleic Acid Enzymology Group](#) at NIEHS. Wilson was very supportive of Cavanaugh's involvement with NTA and OFCD activities, which enabled her to develop communication and leadership skills that are crucial to her current position.

"Dr. Wilson regularly advises his postdoctoral fellows on matters that will help them become independent researchers," Cavanaugh said. "Although I did not pursue a career in bench science, I appreciate the training he gave me and the analytical skills I am able to apply at my new position."



*Along with her work with NTA and OFCD, Cavanaugh also was a contributing writer for the Environmental Factor during the final months of her fellowship at NIEHS. (Photo courtesy of Steve McCaw)*



*Wilson, who was Cavanaugh's science mentor and supervisor, supported her in career development experiences away from the bench. (Photo courtesy of Steve McCaw)*



## The importance of professional networking

Cavanaugh credits her landing the OPA director position to the strong professional network she built while at NIEHS. “Several people in my network informed me of the job opportunity and introduced me to people who were also on the interview committee,” she explained. Her professional network continued to be her source of support and advice throughout the long job application process.

Cavanaugh urges current postdoctoral fellows to actively participate in various career development events at NIEHS, and to familiarize themselves with the institute and its policies. “Both NTA and OFCD provide invaluable leadership and networking opportunities, and being involved is an excellent way to enhance your communication and transferable skills,” she concluded.

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

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## Environmental Polymorphisms Registry gets new leader

*By Robin Arnette*

Since its opening in 2009, the NIEHS [Clinical Research Unit \(CRU\)](#) has steadily expanded the number of research projects and numbers of staff who help facilitate the work. In early October 2012, the CRU welcomed its newest member, Shepherd Schurman, M.D., to the fold. Schurman comes to NIEHS from the National Institute on Aging (NIA) and now serves as the CRU’s staff clinician and head of the [Environmental Polymorphisms Registry \(EPR\)](#).

From the time he was 4 years old, Schurman said he knew he wanted to become a physician-scientist. Both of his parents were fascinated with science and had relatives who were physicians, so they fostered his interest in medicine and genetics. After completing medical school and a residency in internal medicine, he joined the National Human Genome Research Institute (NHGRI) as a research fellow, studying gene therapy and immune deficiency disorders. After moving to NIA, he started working with DNA repair and polymorphisms, or gene differences, associated with age-related diseases.

“When the position of staff clinician came open here, I thought it was a great opportunity,” Schurman said. “I believed it would be a pretty good fit, given my background in genetics, clinical trials, and polymorphisms research.”

Darryl Zeldin, M.D., the NIEHS Scientific Director, hired Schurman for the job. He said, “I am confident that Dr. Schurman will exceed our already high expectations in leading the next phase of the EPR.”



*Schurman is a native of Chicago, Ill., and takes over the position of EPR director from Patricia Chulada, Ph.D. (Photo courtesy of Steve McCaw)*

## Heading the EPR

The CRU is a 14,000 square foot facility on the NIEHS campus that conducts studies to determine how environmental exposures influence disease. The EPR, which is one of several ongoing studies at the CRU, provides access to DNA from more than 17,000 individuals from the North Carolina Triangle region. Participants with polymorphisms of interest may be invited to join follow-up studies that allow researchers to perform basic laboratory experiments, such as cell phenotyping from donated blood, or be asked to participate in more comprehensive clinical-based research. With the addition of the EPR's health and exposure survey, an individual's susceptibility to common conditions, such as asthma, diabetes, cardiovascular disease, cancer, and other illnesses can be associated with investigated polymorphisms.

According to Schurman, the EPR fits nicely within the framework of the new NIEHS strategic plan, because of its focus on translational research. As examples, he mentioned EPR's adherence to goal 1, which seeks to identify mechanisms behind complex disease, and goal 2, which aims to understand individual susceptibility to disease resulting from environmental factors. He also pointed out that the third theme in the strategic plan, translational science, describes perfectly just what the EPR is doing.

"The key passage from that section is 'Environmental health translational research can introduce, into medical decision-making, a new level of information about gene-environment interaction affecting drugs, biologics, infections, and other environmental factors in health and disease,'" he said. "The EPR can be a valuable resource to both intramural and extramural researchers."

As medical director of the CRU, Stavros Garantziotis, M.D., knows that the only way for the EPR to maximize its potential is to get many more researchers to initiate studies using its DNA. Recruiting scientists to mine the EPR's genetic information will be a challenge Garantziotis feels Schurman is ready to meet.

"Dr. Schurman is very well qualified for this role, having worked for many years at the NIA with the Baltimore Longitudinal Study of Aging, as well as having collaborated in the earliest gene treatment trials at the NHGRI," Garantziotis said. "He thus brings a great amalgam of skills and experiences that will enable him to lead the EPR to a new phase, and help us gain new insights into the interaction of genes and the environment in the development of disease."

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## NIEHS employees recognized by NIH OD

*By Eddy Ball*


Ten NIEHS employees were among those recognized Dec. 19 at the 2012 NIH Office of the Director (OD) Honor Award ceremony in the Natcher Auditorium on the NIH campus in Bethesda, Md.



December 19, 2012  
1:59 pm  
Ruth L. Kirschstein Auditorium  
Natcher Conference Center

**Linked video:**  
[People with NIH system access can view an archived video of the ceremony \(01:55:00\)](#)

(Launches in new window)

Download Media Player:  Flash 

On hand to present the awards were NIH Director Francis Collins, M.D., Ph.D., and Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D., who were joined on stage by deputy directors of the respective areas in which recipient employees were honored.

“The OD Honor Award recognizes exceptional contributions by employees to the NIH mission,” said NIH OD Senior Program Advisor Janie Kuhn, who organized the program. The Honor Award ranks with the NIH Merit Award, which can be awarded by directors of institutes and centers, and is often presented in recognition of outstanding performance by employees involved in trans-NIH, U.S. Department of Health and Human Services (DHHS), and other federal initiatives.

**Awardees from NIEHS included the following:**

- Office of Management Program Coordinator **Monya Brace** and Office of Clinical Research Clinical Laboratory Manager **Annette Rice** — 2011 Feds Feed Families Team — In recognition of exemplary efforts in promoting the Fed’s Feed Families Campaign at the National Institutes of Health and throughout the United States.
- Office of Acquisitions Contract Specialist **Antoinette Bridges, D.M.**, Office of Acquisitions Branch Chief **Charles Conrad**, and Administrative Services and Analysis Branch Employee Services Program Specialist **Cynthia Radford** — Appropriations Law Training and Leadership Group — For outstanding achievement in providing alternative offerings, essential communications, tracking, and problem resolution to ensure full compliance with the DHHS Appropriations Law Requirement.
- Office of Technology Transfer Director **Elizabeth Denholm, Ph.D.** — NIH Biospecimen Working Group — For dedication and diligent, persistent efforts, which have resulted in a major overhaul in the reporting of biospecimens at NIH.



*Janice Allen (Photo courtesy of Steve McCaw)*



*Monya Brace (Photo courtesy of Steve McCaw)*



*Antoinette Bridges (Photo courtesy of Steve McCaw)*



*Charles Conrad (Photo courtesy of Steve McCaw)*



*Elizabeth Denholm (Photo courtesy of Steve McCaw)*



*Jane Lambert (Photo courtesy of Steve McCaw)*



- Clinical Research Program Institutional Review Board Administrator **Jane Lambert** — NIH Clinical Research Protocol Application Taskforce — For persistent, outstanding efforts to create and harmonize the contents of the NIH clinical research protocol template.
- Grants Management Branch Grants Management Specialist **Molly Puente, Ph.D.** — Research Performance Progress Report Group — In recognition of exceptional leadership and outstanding efforts in NIH's implementation of the Federal-wide Research Performance Progress Report.
- Scientific Review Branch Health Scientist Administrator **Janice Allen, Ph.D.** — Review Policy Committee Scientific Review Officer Technical Competencies Team — In recognition of exceptional vision, teamwork, and collaboration in identifying Scientific Review Officer Core Technical Competencies.
- Laboratory of Molecular Carcinogenesis Staff Scientist **John Roberts, Ph.D.** — Team for Implementing the Animal Care and Use Guide at NIH — For assuring a future national and international leadership role of the NIH Animal Care and Use Program with the 8th edition of their guide.



*Molly Puente (Photo courtesy of Steve McCaw)*



*Cynthia Radford (Photo courtesy of Steve McCaw)*



*Annette Rice (Photo courtesy of Steve McCaw)*



*John Roberts (Photo courtesy of Steve McCaw)*

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## Stokes honored by U.S. Public Health Service

*By Eddy Ball*

NTP center director Rear Adm. William Stokes, D.V.M., received the Distinguished Service Medal from the U.S. Public Health Service (USPHS) Dec. 19, 2012, during his flag officer retirement ceremony at NIEHS. The [event](#) filled Rodbell auditorium with well-wishers, including members of his family, many of his co-workers in NTP, and more than 70 fellow USPHS officers in dress uniform.

The Distinguished Service Medal is the highest award presented by USPHS, and the flag officer retirement ceremony is a time-honored tradition of the USPHS, based on the centuries-old pomp and circumstance of maritime changing-of-command formalities. On hand to support the carefully choreographed event were the U.S. Surgeon General's Honor Cadre, USPHS Choral Ensemble, and U.S. Army Forces Command Brass Quintet.

Stokes' retirement as a rear admiral and assistant U.S. Surgeon General, with nearly 34 years of active duty service as a commissioned officer, was mandated by USPHS regulations.

### High praise for a stellar career

On stage with Stokes during the 2 1/2-hour event were NIEHS/ NTP Director Linda Birnbaum, Ph.D.; NTP Associate Director John Bucher, Ph.D.; Deputy U.S. Surgeon General Boris Lushniak, M.D.; and fellow officers who had served with Stokes during the course of his career as a USPHS commissioned officer.

Master of Ceremony USPHS Commander George Durgin, Resilience Division chief at the Defense Centers of Excellence introduced the program of nine speakers who delivered the highest praise for their retiring colleague. Captain Terri Clark, D.V.M., the tenth chief veterinary officer for USPHS and director of the NIH Office of Animal Care and Use, set the tone for those who followed her. "Bill is just a steadfast visionary leader," she said of her mentor and longtime comrade.

Others praised Stokes for his work in disaster deployments, including the 2005 aftermath of Hurricane Katrina; his important contributions during the transformation of USPHS to a more consistently military-like uniformed service; and his selfless efforts to spur the career development of subordinates and colleagues. The ceremony included the reading of letters from the assistant secretary of the U.S. Department of Health and Human Services, former U.S. Surgeon General Richard Carmona, M.D., members of the North Carolina congressional delegation, and a number of colleagues who were unable to attend.

Lushniak offered the ultimate praise from a commanding officer, when he said of Stokes, "If you want a job done the right way, put Bill in charge."

Emotions run high at this important point in an officer's career, and it was hardly surprising that Stokes had to pause several times when his turn came to speak. Facing the sea of blue uniforms, Stokes recalled fondly the many role models who, during his life, helped to build his strong work ethic and instill, early on, the core values of USPHS — integrity, excellence, leadership, and service to others.



*Stokes, above, and the other uniformed speakers saluted briskly as they received military honors and entered the auditorium to make their way to the stage. (Photo courtesy of Steve McCaw)*



*The U.S. Surgeon General's Honor Cadre presented the colors, as well as performed the symbolic retirement of Stokes' Assistant Surgeon General flag and the Old Glory tribute. (Photo courtesy of Steve McCaw)*



Stokes received USPHS and U.S. flags, as symbols of his dedicated service, as well as gifts from colleagues. In an especially touching part of the ceremony, Lushniak presented Stokes' wife, Nancy, with a citation and flowers in appreciation of her support during what Lushniak described as Stokes' marathon of service to the nation's public health.

### Stokes' legacy at NIH

Prior to his official separation Dec. 31, 2012, Stokes served as director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and executive director of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). NICEATM and ICCVAM provide scientific support and coordinate interagency initiatives for advancing new and alternative safety testing methods, including those designed to replace, reduce, and refine the use of animals in toxicity testing.

Stokes has 33 years of experience in biomedical and toxicological research, 26 years of that with NIH, and has served the NTP since 1992. He served his country in three of the seven uniformed services, for a total of 42 years of active duty and reserve service. He also held positions as the animal program director at NIEHS and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and as the eighth chief veterinary officer for USPHS.



*As master of ceremony, Durgin set the tone for the event with his gravitas and defined the military cadence of the ceremony with the staccato emphasis of his delivery. (Photo courtesy of Steve McCaw)*



*Lushniak was energetic, humorous, and candid, as he described the changes officers face as they move from active duty as health warriors on call virtually 24 hours a day to officers at ease awaiting orders that may not come. Turning to face Stokes, Lushniak said, "This ain't gonna be easy for you." (Photo courtesy of Steve McCaw)*



*Stokes' family members enjoyed a place of honor on the front row of the audience. His wife, Nancy, right, was also honored for her support of her husband's career, especially during the times he was deployed and absent from the home. (Photo courtesy of Steve McCaw)*





*Following their own tributes to their colleague, Bucher, left, and Birnbaum had an opportunity to enjoy the comic relief Stokes' uniformed colleagues and friends added to this generally solemn ceremony. (Photo courtesy of Steve McCaw)*



*In one of his final acts as NIEHS chief of staff, Captain Paul Jung, M.D., read letters of congratulations from the North Carolina congressional delegation. Jung assumed the position of deputy director of the newly formed headquarters for the USPHS Commissioned Corps in Rockville, Md., Jan. 1. (Photo courtesy of Steve McCaw)*



*In a moving tribute to Old Glory and the long history of selfless sacrifice to country on the part of uniformed officers, Stokes received his retirement national ensign that had flown at several of his duty stations, including NIEHS. (Photo courtesy of Steve McCaw)*



*Warren Casey, Ph.D., who assumes the role of acting director of NICEATM with Stokes' transition, was among the many NTP colleagues on hand to congratulate and thank him for his long service to the cause of alternative testing. Casey joined NICEATM as deputy director in 2010. (Photo courtesy of Steve McCaw)*



*The ceremony concluded with the speakers and the audiences standing in respect as Stokes received his symbolic permission to go ashore. Following the benediction, attendees gathered for a reception in the NIEHS cafeteria. (Photo courtesy of Steve McCaw)*

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# Science Notebook

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## 2012 papers of the year

From the nearly 2,500 NIEHS-funded studies published in 2012, leaders of the Institute's three research divisions selected 30 for special recognition as Papers of the Year.

### Research funded by grants (click title for abstract)

- [Non-coding DNA variants may link early exposures with later health problems](#)
- [Reversible epigenetic changes associated with bee behavior](#)
- [Triclosan impairs heart and skeletal muscle contractility](#)
- [Whole genome sequencing reveals genetic basis for diversity and evolution](#)
- [Gene variants linked with faster Parkinson's disease progression](#)
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- [Autism risk linked to maternal diabetes and obesity](#)
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- [Menthol lessens irritation from cigarette smoke](#)
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### In-house research (click title for abstract)

- [EET research may help in the fight against cancer](#)
- [Calcium influx is a critical component of embryonic development](#)
- [Pol II pausing modulates basal gene expression in signal transduction cascades](#)
- [Clustered mutations attributed to body's natural defenses](#)
- [Fertility drugs and young-onset breast cancer](#)
- [Cerium dioxide nanoparticles may lead to human immune cell death](#)

- [New treatment allows medicines to cross blood-brain barrier](#)
- [Glucocorticoid signaling could lead to better therapeutics](#)
- [Bacteria in house dust worsens asthma](#)
- [Mechanisms of anticancer drug resistance](#)

## **National Toxicology Program research (click title for abstract)**

- [Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype](#)
- [Testing an aflatoxin B1 gene signature in rat archival tissues](#)
- [Hepatocellular carcinomas in B6C3F1 mice treated with Ginkgo biloba extract for two-years differ from spontaneous liver tumors in cancer gene mutations and genomic pathways](#)
- [An ethanolic extract of black cohosh causes hematological changes but not estrogenic effects in female rodents](#)
- [The genome architecture of the Collaborative Cross mouse genetic reference population](#)

## **Research funded by grants**

### **Non-coding DNA variants may link early exposures with later health problems**

Researchers, supported in part by NIEHS, report that genetic differences linked to a variety of diseases are activated during fetal development. These findings could help explain why some early environmental exposures increase disease risk years or even decades later.

The researchers investigated whether variants in noncoding regions of DNA regulate gene expression, by looking at thousands of these variants identified in genome-wide association studies (GWAS). The researchers also identified the genes regulated by hundreds of GWAS variants, including genes associated with several diseases. Almost 80 percent of GWAS variants in regulatory DNA were connected to genes that were not the closest ones to the variant, which is probably why previous attempts to link GWAS variants with target genes have been so difficult.

*Citation:* [Maurano MT, Humbert R, Rynes E, Thurman RE, Haugen E, Wang H, Reynolds AP, Sandstrom R, Qu H, Brody J, Shafer A, Neri F, Lee K, Kuttyavin T, Stehling-Sun S, Johnson AK, Canfield TK, Giste E, Diegel M, Bates D, Hansen RS, Neph S, Sabo PJ, Heimfeld S, Raubitschek A, Ziegler S, Cotsapas C, Sotoodehnia N, Glass I, Sunyaev SR, Kaul R, Stamatoyannopoulos JA. 2012. Systematic localization of common disease-associated variation in regulatory DNA. Science 337\(6099\):1190-1195.](#)

[synopsis]

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## Reversible epigenetic changes associated with bee behavior

Researchers studying honeybees report what could be the first evidence of reversible epigenetic changes associated with behavior. The research may shed light on problems that people have with learning, memory, stress response, and mood disorders, which all involve interactions between genetic and epigenetic components. The work was supported by an NIH Director's Pioneer Award.

The researchers found no differences in DNA methylation between worker and queen bees, roles that are irreversible. However, they saw substantial differences between nurses and forager bees. Reverting foragers back to nurses reestablished methylation levels for a majority of genes, providing evidence of reversible epigenetic changes that are associated with behavior.

*Citation:* [Herb BR, Wolschin F, Hansen KD, Aryee MJ, Langmead B, Irizarry R, Amdam GV, Feinberg AP. 2012. Reversible switching between epigenetic states in honeybee behavioral subcastes. Nat Neurosci 15\(10\):1371-1373.](#)

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## Triclosan impairs heart and skeletal muscle contractility

NIEHS grantees report that triclosan hinders muscle contractions at a cellular level and also causes muscle problems in fish and mice. Triclosan is an antibacterial agent widely used in personal-care products such as hand soap and toothpaste, and it has been detected in waterways and fish. This new study provides evidence of the chemical's potentially negative effects on human and environmental health and also reveals a mechanism for these effects.

Mice given a single dose of triclosan showed an 18-percent reduction in grip strength for up to 60 minutes. Minnows exposed to triclosan in the water for seven days showed significantly reduced swimming activity compared to controls.

*Citation:* [Cherednichenko G, Zhang R, Bannister RA, Timofeyev V, Li N, Fritsch EB, Feng W, Barrientos GC, Schebb NH, Hammock BD, Beam KG, Chiamvimonvat N, Pessah IN. 2012. Triclosan impairs excitation-contraction coupling and Ca<sup>2+</sup> dynamics in striated muscle. Proc Natl Acad Sci U S A 109\(35\):14158-14163.](#)

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## Whole genome sequencing reveals genetic basis for diversity and evolution

In one of the first population genomics studies to use high-coverage whole-genome sequencing, NIEHS-supported researchers analyzed the genomes of 15 Africans from three different hunter-gatherer groups.

The work reveals new insight into human diversity and evolution and also shows the potential of new genome sequencing technology for uncovering the genetic basis of normal variations in humans and for identifying the genetic basis of disease risk.

The results from the genome analysis provide evidence that the direct ancestors of modern humans might have interbred with members of an unknown ancestral group of hominins and that different groups evolved distinctly. The work also identifies new candidate genes that are likely involved in making Pygmies short in stature.

*Citation:* Lachance J, Vernot B, Elbers CC, Ferwerda B, Froment A, Bodo JM, Lema G, Fu W, Nyambo TB, Rebbeck TR, Zhang K, Akey JM, Tishkoff SA. 2012. Evolutionary history and adaptation from high-coverage whole-genome sequences of diverse African hunter-gatherers. *Cell* 150(3):457-469.

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## Gene variants linked with faster Parkinson's disease progression

NIEHS grantees report that Parkinson's disease patients with two specific variants of the alpha-synuclein gene progressed toward motor decline significantly faster than patients without these variants. This work could lead to new therapies and help identify those who would benefit most from early intervention.

Although the findings need replication in other well-characterized Parkinson's disease populations, the researchers say that their work shows that these gene variants could be used to identify patients who will likely experience faster disease progression. The work also points to the alpha-synuclein pathway as a promising potential therapeutic target.

*Citation:* Ritz B, Rhodes SL, Bordelon Y, Bronstein J. 2012. Alpha-synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. *PLoS One* 7(5):e36199.

[\[synopsis\]](#)

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## Cardiovascular effects of Beijing Olympics air pollution reduction

The Chinese government shut down factories and limited automobile traffic during the Beijing Olympics, to lessen air pollution. These temporary changes in air pollution levels were associated with acute changes in cardiovascular biomarkers in healthy young people, according to a study from NIEHS grantees. The research adds evidence that higher levels of air pollution are linked with an increased risk of cardiovascular problems.

During the Olympics, the study participants showed significant reductions in von Willebrand factor and soluble CD62P levels, which are both associated with blood coagulation. Soluble CD62P and systolic blood pressure levels increased significantly once the pollution controls were lifted after the Olympics.

*Citation:* Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, Ohman-Strickland P, Hu M, Philipp C, Diehl SR, Lu SE, Tong J, Gong J, Thomas D, Zhu T, Zhang JJ. 2012. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA 307(19):2068-2078.

[\[synopsis\]](#) [\[story\]](#)

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## Environmental exposures influence behavior of later generations

A new NIEHS-funded study shows that animals whose ancestors were exposed to a fungicide have a more profound reaction to stress than the offspring of unexposed animals. The work demonstrates that an ancestor's exposure can influence the stress response of future generations.

The authors of the study used a systems biology approach by examining genetic and molecular changes in the brain as well as behavior. They exposed gestating female rats to the fungicide vinclozolin and later performed testing on the third generation of offspring. When exposed to stress during adolescence, the offspring of exposed rats had greater anxiety, sensitivity to stress, and more activity in stress-related regions of the brain.

*Citation:* Crews D, Gillette R, Scarpino SV, Manikkam M, Savenkova MI, Skinner MK. 2012. Epigenetic transgenerational inheritance of altered stress responses. Proc Natl Acad Sci U S A 109(23):9143-9148.

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## Autism risk linked to maternal diabetes and obesity

Findings from the NIEHS-funded Childhood Autism Risks from Genetics and the Environment (CHARGE) study provide evidence that maternal metabolic conditions can increase the risk for autism, as well as developmental delay without autistic symptoms. The findings suggest that fetal exposure to elevated levels of glucose and maternal inflammation adversely affect fetal development.

The metabolic conditions studied included obesity or hypertension at the start of pregnancy, or diabetes during pregnancy, which were linked with significantly increased risk for having a child with autism or other developmental disorders. In addition, children with autism spectrum disorder and diabetic mothers had greater deficits in adaptive communication, language comprehension, and language production than children with autism spectrum disorder born to healthy mothers.

*Citation:* Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, Hertz-Picciotto I. 2012. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 129(5):e1121-1128.

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## Health implications of temperature variability

Climate change is expected to bring increasing variability in summer temperatures, which could shorten life expectancy for older people with chronic medical conditions, according to an NIEHS-funded study. Although other studies have looked at the short-term effects of heat waves, this study examined the long-term effects of climate change on life expectancy.

The researchers used Medicare data from 1985 to 2006 to follow the health of 3.7 million chronically ill people over age 65. They studied whether mortality related to variability in summer temperature in 125 cities and took into account other factors, such as winter temperature variance, ozone levels, and individual risk factors. They compiled results for 125 individual cities and then pooled the results.

*Citation:* [Zanobetti A, O'Neill MS, Gronlund CJ, Schwartz JD](#). 2012. Summer temperature variability and long-term survival among elderly people with chronic disease. *Proc Natl Acad Sci U S A* 109(17):6608-6613.

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## Air pollution linked to cognitive decline

In one of the first studies of its kind, NIEHS grantees report that a significantly faster decline in the cognitive function of older women is associated with long-term exposure to particulate matter (PM) air pollution at levels typical of many areas of the U.S.

The researchers estimate that a 10-microgram per cubic meter increase in long-term PM exposure was cognitively equivalent to aging by approximately two years. If the findings are confirmed in other studies, reducing air pollution could offer a way to lessen age-related cognitive decline and, because cognitive decline often precedes the development of dementia, a way to reduce the future population burden of dementia.

*Citation:* [Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F](#). 2012. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med* 172(3):219-227.

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## The cost of asthma from traffic-related air pollution

NIEHS-funded researchers have estimated that childhood asthma associated with air pollution in Long Beach and Riverside, Calif., costs \$18 million each year.

Using a new method that researchers say more accurately estimates the overall burden of asthma and the costs associated with air pollution, they calculated the total annual cost for a typical asthma case to be \$3,819 in Long Beach and \$4,063 in Riverside. The largest portion of this cost came from asthma-related school absences, which often require that parents or caregivers miss work. The investigators say that their new method takes into account the full impact of traffic-related pollution and can be applied to other urban areas.

*Citation:* [Brandt SJ, Perez L, Künzli N, Lurmann F, McConnell R](#). 2012. Costs of childhood asthma due to traffic-related pollution in two California communities. *Eur Respir J* 40(2):363-70.

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## Menthol lessens irritation from cigarette smoke

An NIEHS-supported study has shown that menthol, the cooling agent in peppermint, counteracts the irritating effects of cigarette smoke constituents. The researchers studied acrolein, acetic acid, and cyclohexanone, which are irritating components of cigarette smoke that vary widely in their chemical structure and biological properties. The experiments demonstrated that menthol's counterirritant effects resulted from activation of the chemical receptor TRPM8.

By suppressing reactions such as coughing, menthol could increase the amount of smoke inhaled and thus promote addiction to nicotine. The 2009 Family Smoking Prevention and Tobacco Control Act banned flavored tobacco additives but exempted menthol while the U.S. Food and Drug Administration evaluated scientific data.

*Citation:* [Willis DN, Liu B, Ha MA, Jordt SE, Morris JB](#). 2011. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. *FASEB J* 25(12):4434-4444.

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## Perfluorinated compounds and immune response in children

Research funded by NIEHS has shown that elevated exposure to perfluorinated compounds was associated with reduced immune responses in children.

The prospective study found that children with elevated exposure to perfluorinated compounds had lower antibody responses to childhood immunizations. The antibody response to childhood immunization reflects how well the immune system is functioning. The researchers report that this study is one of the first to link childhood exposure to perfluorinated compounds with immune system deficiency. The results point to the importance of assessing the immunotoxic potential of these compounds, which are highly persistent and can contaminate drinking water, as well as food.

*Citation:* [Grandjean P, Anderson EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P, Heilmann C](#). 2012. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA* 307(4):391-397.

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## Rice consumption and arsenic exposure in pregnant women

NIEHS grantees report that urinary arsenic concentrations were higher for pregnant women who had recently consumed rice than for those who had not. The findings highlight the need to monitor arsenic levels in food.

The researchers tested for arsenic in the urine of 229 pregnant women in New Hampshire, 73 of whom reported eating rice during the two days before urine collection. The arsenic concentration of the tap water in the women's homes was also tested to identify any exposure from drinking water. The women who reported eating rice during the two days prior to urine collection had a median total urinary arsenic concentration of 5.27 micrograms per liter, which was significantly different from the 3.38 micrograms per liter median concentration for those who did not consume rice.

The researchers note the need for more research to determine any health impacts of this source of exposure. Any identified health risks will also need to be weighed against the nutritional benefits of eating rice.

*Citation:* Gilbert-Diamond D, Cottingham KL, Gruber JF, Punshon T, Sayarath V, Gandolfi AJ, Baker ER, Jackson BP, Folt CL, Karagas MR. 2011. Rice consumption contributes to arsenic exposure in US women. *Proc Natl Acad Sci U S A* 108(51): 20656-20660.

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## Consuming canned soup linked to higher BPA levels

Researchers funded by NIEHS found that a group of volunteers who consumed a serving of canned soup every day for five days had more than a 1,000 percent increase in urinary bisphenol A (BPA) concentrations than when the same individuals consumed fresh soup daily for five days.

Eating a serving of canned soup daily was associated with a 1,221 percent increase in BPA concentration compared to levels in urine collected after consumption of fresh soup. Even though the elevation in urinary BPA concentrations might be temporary, the researchers comment that their findings could be important, especially as more and improved alternatives to epoxy linings are developed.

*Citation:* Carwile JL, Ye X, Zhou X, Calafat AM, Michels KB. 2011. Canned soup consumption and urinary bisphenol A: a randomized crossover trial. *JAMA* 306(20):2218-2220.

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## In-house research

### EET research may help in the fight against cancer

A collaborative team of NIEHS-funded scientists has found that the removal of small molecules produced in the body called epoxyeicosatrienoic acids (EETs) may prevent the formation of blood vessels that feed tumor cells.

High levels of EETs are beneficial in patients with diseases, such as hypertension, heart attack, and stroke, because the molecules cause blood vessels to dilate. However, the team determined for the first time that EETs in the healthy tissue surrounding the tumors also work with a protein known to induce blood vessel growth, called vascular endothelial growth factor, to activate blood vessel formation that feeds tumors. Mice in the experiments with higher EETs produced more metastatic tumors than mice with lower EETs.

*Citation:* Panigrahy D, Edin ML, Lee CR, Huang S, Bielenberg DR, Butterfield CE, Barnés CM, Mammoto A, Mammoto T, Luria A, Benny O, Chaponis DM, Dudley AC, Greene ER, Vergilio JA, Pietramaggiori G, Scherer-Pietramaggiori SS, Short SM, Seth M, Lih FB, Tomer KB, Yang J, Schwendener RA, Hammock BD, Falck JR, Manthathi VL, Ingber DE, Kaipainen A, D'Amore PA, Kieran MW, Zeldin DC. 2012. Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *J Clin Invest* 122(1):178-191.

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### Calcium influx is a critical component of embryonic development

Upon fertilization by the sperm, repetitive calcium oscillations occur as a result of the movement of calcium from egg storage or outside the cell, into the egg cytoplasm, and then back into storage or out of the egg. These calcium oscillations are essential for mammalian egg activation and the early stages of embryonic development.

NIEHS scientists determined that some of the signaling pathways induced by calcium movements take place directly under the egg's plasma membrane, rather than entirely inside of the egg. The research has far-reaching implications for clinically assisted reproduction and fertility preservation technologies, since defects in calcium signaling at fertilization can result in a failure of the embryo to implant or develop to term.

*Citation:* Miao YL, Stein P, Jefferson WN, Padilla-Banks E, Williams CJ. 2012. Calcium influx-mediated signaling is required for complete mouse egg activation. *Proc Natl Acad Sci U S A* 109(11):4169-4174.

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### Pol II pausing modulates basal gene expression in signal transduction cascades

NIEHS scientists have revealed that RNA polymerase II (Pol II) pausing does not necessarily lead to higher gene expression upon induction of stimulus-responsive networks. Rather, it is important in modulating basal gene expression. The research offers a new model for understanding how paused Pol II impacts gene expression in resting cells.

The researchers found that many downstream target genes were rapidly induced, despite not harboring paused Pol II at their promoters prior to pathogenic challenge. Their findings indicate that, although the regulatory components are more modestly expressed in response to immune challenge, their basal expression in resting cells is more tightly regulated so that these cells are better poised to rapidly initiate the immune response cascade as needed.

*Citation:* [Gilchrist DA](#), [Fromm G](#), [dos Santos G](#), [Pham LN](#), [McDaniel IE](#), [Burkholder A](#), [Fargo DC](#), [Adelman K](#). 2012. Regulating the regulators: the pervasive effects of Pol II pausing on stimulus-responsive gene networks. *Genes Dev* 26(9):933-944.

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## Clustered mutations attributed to body's natural defenses

A team of NIEHS-funded scientists has identified DNA regions with a high number of nonrandom mutations in yeast and some human cancers. Contrary to the traditionally held view that mutations occur randomly, these mutations were not caused by environmental damage, but by a specific set of proteins known as APOBEC cytosine-deaminases, which are part of the human immune system's response to viruses that enter the body.

The research team developed bioinformatics tools to determine if human cancers contained similar mutation clusters similar to those found in yeast and, surprisingly, nearly half of them did. The results of this study suggest that several antiviral drugs, capable of stimulating APOBEC genes, should be considered potential mutagens.

*Citation:* [Roberts SA](#), [Sterling J](#), [Thompson C](#), [Harris S](#), [Mav D](#), [Shah R](#), [Klimczak LJ](#), [Kryukov GV](#), [Malc E](#), [Mieczkowski PA](#), [Resnick MA](#), [Gordenin DA](#). 2012. Clustered mutations in yeast and in human cancers can arise from damaged long single-strand DNA regions. *Mol Cell* 46(4):424-435.

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## Fertility drugs and young-onset breast cancer

Among participants in the NIEHS Two Sister Study, funded in part by Susan G. Komen for the Cure, women who had used ovary-stimulating fertility drugs, clomiphene citrate or follicle-stimulating hormone, without getting pregnant, had reduced risk of young-onset breast cancer.

Participants were pairs of sisters, one of whom had been diagnosed with breast cancer before the age of 50. They were categorized based on whether they had used ovulation-stimulating fertility drugs and whether pregnancy had resulted. Unlike previous studies, the Two Sister Study distinguished between fertility treatments that produced pregnancy versus those that did not. Moreover, use of sisters who are well-matched for many factors allows for a fair comparison.

*Citation:* [Fei C](#), [DeRoo LA](#), [Sandler DP](#), [Weinberg CR](#). 2012. Fertility drugs and young-onset breast cancer: Results from the Two Sister Study. *J Natl Cancer Inst* 104(13):1021-1027.

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## Cerium dioxide nanoparticles may lead to human immune cell death

A new study by NIEHS researchers using human peripheral blood monocytes from healthy donors shows that cerium dioxide (CeO<sub>2</sub>) nanoparticles at environmentally relevant exposure levels causes cell death via apoptosis and autophagy. It is the first report on the effects of CeO<sub>2</sub> nanoparticles in primary human cells. Given the fact that CeO<sub>2</sub> emissions from diesel fuel are estimated to reach 22 million pounds per year in Europe, it is vital to understand their potential impact on human health.

The apoptotic mechanism was independent of caspase activation, but dependent on mitochondrial damage and induction of apoptosis-inducing factor. Cell death was also mediated through autophagy, which increased if the p53 tumor suppressor protein was inhibited.

*Citation:* [Hussain S, Al-Nsour F, Rice AB, Marshburn J, Yingling B, Ji Z, Zink JI, Walker NJ, Garantziotis S. 2012. Cerium dioxide nanoparticles induce apoptosis and autophagy in human peripheral blood monocytes. ACS Nano 6\(7\):5820-5829.](#)

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## New treatment allows medicines to cross blood-brain barrier

A study by NIEHS researchers identified a signaling pathway that reduces the transport activity of P-glycoprotein, an ATP-driven drug efflux pump in rat brain capillaries known to be a major obstacle to delivering medicines to the brain. The work may lead to new treatments for brain and spinal cord injury, brain cancer, and epilepsy in humans.

The research team used a confocal microscopy-based assay to identify a signaling pathway that abolished P-glycoprotein transport activity without changing transporter protein expression. These findings were validated in vivo and led the researchers to conclude that reducing P-glycoprotein activity can allow small molecule pharmaceuticals to safely cross the blood-brain barrier.

*Citation:* [Cannon RE, Peart JC, Hawkins BT, Campos CR, Miller DS. 2012. Targeting blood-brain barrier sphingolipid signaling reduces basal P-glycoprotein activity and improves drug delivery to the brain. Proc Natl Acad Sci U S A 109\(39\):15930-15935.](#)

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## Glucocorticoid signaling could lead to better therapeutics

NIEHS scientists have determined that glucocorticoids modulate the signaling profile of G protein-coupled receptors (GPCRs) through alterations in arrestin gene expression. Since GPCRs are targeted by nearly half of all prescription drugs, the work could result in the development of specific treatments that will reduce side effects and boost efficacy.



The activity of GPCRs is governed by a group of adaptor proteins called arrestins. Using several different cell types, the research team discovered that glucocorticoids directly regulate arrestin gene expression. The fluctuation in arrestin expression can modify the effect GPCRs can have on human cells by biasing their signaling profile to favor G protein-dependent or beta-arrestin-dependent responses.

*Citation:* [Oakley RH, Revollo J, Cidlowski JA](#). 2012. Glucocorticoids regulate arrestin gene expression and redirect the signaling profile of G protein-coupled receptors. *Proc Natl Acad Sci U S A* 109(43):17591-17596.

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## Bacteria in house dust worsens asthma

NIEHS scientists found that flagellin (FLA), a bacterial protein found in house dust, exacerbates asthma by inducing allergic responses to allergens. The findings, which were confirmed in a human study, reinforce the connection between asthma and the environment.

Inhalation of FLA or house dust extracts containing FLA together with chicken ovalbumin (OVA) caused mice in the study to develop allergic pulmonary inflammation following OVA challenge. The research team also found that the mammalian receptor for FLA, toll-like receptor 5 (TLR5), was required for priming of strong allergic responses in mice by some house dust extracts. The study concluded that household FLA promotes the development of allergic asthma by TLR5-dependent priming.

*Citation:* [Wilson RH, Maruoka S, Whitehead GS, Foley JF, Flake GP, Sever ML, Zeldin DC, Kraft M, Garantziotis S, Nakano H, Cook DN](#). 2012. The Toll-like receptor 5 ligand flagellin promotes asthma by priming allergic responses to indoor allergens. *Nat Med* 18(11):1705-1710.

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## Mechanisms of anticancer drug resistance

NIEHS scientists described the molecular mechanisms by which topoisomerase II (topo II)-DNA adducts are repaired by the mammalian tyrosyl-DNA phosphodiesterase 2 (Tdp2) enzyme. Since some of the most successful cancer chemotherapeutics work by inducing topo II-DNA adducts that promote cancer cell death, this study determines how Tdp2, in turn, contributes to anticancer drug resistance through its topo II-DNA adduct repair functions.

By defining the protein-DNA conjugate processing mechanism at the atomic level, the team determined that Tdp2 dictates a repair pathway by recognizing and removing these topo II-DNA adducts. These findings have future implications in devising strategies to prevent anticancer drug resistance by targeting Tdp2 and developing Tdp2 inhibitors.

*Citation:* [Schellenberg MJ](#), [Appel CD](#), [Adhikari S](#), [Robertson PD](#), [Ramsden DA](#), [Williams RS](#). 2012. Mechanism of repair of 5'-topoisomerase II-DNA adducts by mammalian tyrosyl-DNA phosphodiesterase 2. *Nat Struct Mol Biol* 19(12):1363-1371.

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## National Toxicology Program research

### **Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype**

Researchers explored the hypothesis that the repeated demonstrations of arsenic-induced cancer stem cell (CSC) overabundance in tumors and multiplicity of primary tumors may be explained by an ability of arsenic transformed cells to recruit normal stem cells (NSCs) into CSCs.

The scientists placed arsenic-induced malignant epithelial cells (MECs) in noncontact co-culture by using inserts with normal stem cells (NSC) and assessed the NSCs for malignant transformation. The NSCs rapidly acquired physical (invasion, colony formation, MMP secretion) and molecular characteristics of CSCs. The results showed arsenic-transformed MECs recruited NSCs into CSCs at a significant distance (50-100 cell wide) and had an impact on cancer growth, dissemination, and field canceration.

*Citation:* [Xu Y](#), [Tokar EJ](#), [Sun Y](#), [Waalkes MP](#). 2012. Arsenic-Transformed Malignant Prostate Epithelia Can Convert Noncontiguous Normal Stem Cells into an Oncogenic Phenotype. *Environ Health Perspect* 120(6):865-871.

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### **Testing an aflatoxin B1 gene signature in rat archival tissues**

Formalin-fixed and paraffin-embedded (FFPE) tissues from toxicology studies are a valuable resource for linking histopathological diagnosis to gene expression profiles for insights into molecular mechanisms of chemical pathologies and disease.

Fourteen genes that represent cell cycle progression, response to DNA damage, xenosensor and detoxication systems were evaluated by quantitative PCR in FFPE tissues and corresponding fresh frozen liver samples from male rats treated for 90 days with aflatoxin B1, a liver carcinogen, and concurrent control animals. The resulting data demonstrate that it is now possible to conduct retrospective evaluations of gene signatures in archival tissues. Archival toxicogenomics will reduce animal use by allowing for prior toxicology studies to be interrogated for critical molecular events in chemically induced disease.

*Citation:* [Merrick BA, Auerbach SS, Stockton PS, Foley JF, Malarkey DE, Sills RC, Irwin RD, Tice RR. 2012. Testing an aflatoxin B1 gene signature in rat archival tissues. Chem Res Toxicol 25\(5\):1132-1144.](#)

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## **Hepatocellular carcinomas in B6C3F1 mice treated with Ginkgo biloba extract for two-years differ from spontaneous liver tumors in cancer gene mutations and genomic pathways**

This study provides a molecular context for the genetic changes associated with hepatocarcinogenesis in *Ginkgo biloba* leaf extract (GBE)-exposed mice and illustrates the marked differences between these tumors and those arising spontaneously in the B6C3F1 mouse.

The molecular changes observed in hepatocellular carcinoma (HCC) from GBE-treated animals may be of relevance to those seen in human HCC and other types of cancer. Although a significant amount of data is present in the scientific literature pertaining to the reported health benefits of GBE use, these findings suggest that with long term use of high doses of GBE there may be potential health risks, and it is therefore important that the health status of individuals on chronic GBE therapy is monitored.

*Citation:* [Hoenerhoff MJ, Pandiri AR, Snyder SA, Hong HH, Ton T-V, Peddada S, Shockley KR, Witt K, Chan P, Rider C, Kooistra L, Nyska A, Sills RC. 2012. Hepatocellular carcinomas in B6C3F1 mice treated with Ginkgo biloba extract for two-years differ from spontaneous liver tumors in cancer gene mutations and genomic pathways. Toxicol Pathol; doi:10.1177/0192623312467520 \[Online 21 December 2012\].](#)

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## **An ethanolic extract of black cohosh causes hematological changes but not estrogenic effects in female rodents**

Black cohosh extract (BCE) is used as a remedy for pain and gynecological ailments, and modern preparations are commonly sold as ethanolic extracts available as dietary supplements. In this first study of its kind, researchers used rodent models to characterize the general toxicity of BCE and address suspected estrogenic and anti-estrogenic activity.

BCE induced dose-dependent hematological changes consistent with a non-regenerative macrocytic anemia and increased frequencies of peripheral micronucleated red blood cells. Effects were more severe in mice — seen at all exposure dose levels — than rats. Dose-dependent thymus and liver toxicity was also observed in rats. Apparent effects on puberty were observed, but were not associated with alteration in estrogenic and anti-estrogenic activity.

*Citation:* [Mercado-Feliciano M, Cora MC, Witt KL, Granville CA, Hejtmancik MR, Fomby L, Knostman KA, Ryan MJ, Newbold R, Smith C, Foster PM, Vallant MK, Stout MD. 2012. An ethanolic extract of black cohosh causes hematological changes but not estrogenic effects in female rodents. Toxicol Appl Pharmacol 263\(2\):138-147.](#)

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# The genome architecture of the Collaborative Cross mouse genetic reference population

The Collaborative Cross Consortium, which includes NTP scientist Jef French, Ph.D., reports on the development of a unique genetic resource population, the Collaborative Cross (CC), a multiparental recombinant inbred panel derived from eight laboratory mouse inbred strains using mice from The Jackson Laboratory, involved the University of North Carolina, Tel Aviv University, and Geniad in Australia.

The report includes information on access to the CC population and to the associated raw data describing the genetic structure of individual lines. Integration of rich phenotypic and genomic data over time and across a wide variety of fields will be vital to delivering on one of the key attributes of the CC, a common genetic reference platform for identifying causative variants and genetic networks determining traits in mammals.

*Citation:* [Collaborative Cross Consortium](#). 2012. The genome architecture of the Collaborative Cross mouse genetic reference population. *Genetics* 190(2):389-401.

(The contributing writer for Extramural summaries was Nancy D. Lamontagne a science writer with MDB, Inc., a contractor for the NIEHS Division of Extramural Research and Training, Superfund Research Program, and Worker Education and Training Program.

Intramural summaries were written by Mamta Behl, Ph.D., a contract neurotoxicologist in the NTP Toxicology Branch; Nisha Cavanaugh, Ph.D., a former Intramural Research Training Award (IRTA) postdoctoral fellow in the NIEHS Laboratory of Structural Biology DNA Repair and Nucleic Acid Enzymology Group; Raluca Dumitru, M.D., Ph.D., a former Intramural Research Training Award fellow in the NIEHS Laboratory of Molecular Carcinogenesis Stem Cell Biology Group; Brant Hamel Ph.D., a former IRTA fellow in the NIEHS Laboratory of Signal Transduction Molecular Endocrinology Group; Melissa Kerr, a chemistry student at North Carolina Central University and intern in the NIEHS Office of Communications and Public Liaison; Anshul Pandya, Ph.D., a former IRTA fellow in the Laboratory of Neurobiology Ion Channel Physiology Group; Sonika Patial, D.V.M., Ph.D., a visiting fellow in the Laboratory of Signal Transduction Polypeptide Hormone Action Group; Bhargavi Rao, Ph.D., an IRTA fellow in the NIEHS Laboratory of Molecular Carcinogenesis Chromatin and Gene Expression Group; Jeffrey Stumpf, Ph.D., a former IRTA Fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group; Sheetal Thakur, Ph.D., an IRTA fellow in the NIEHS/NTP Toxicology Branch; Ian Thomas, a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor; Darshini Trivedi, Ph.D., an IRTA fellow in the NIEH Laboratory of Toxicology and Pharmacology Metabolism and Molecular Mechanisms Group; Sheila Yong, Ph.D., a visiting fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group; and Emily Zhou, Ph.D., a former research fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.

Authors of the NTP Papers of the Year contributed their summaries, which were submitted by their NTP branch chiefs.)

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# NTP board gives go ahead for PAH research and systematic review

*By Robin Mackar*

When the NTP Board of Scientific Counselors (BSC) met on Dec. 11, 2012, two main agenda items took center stage — polycyclic aromatic hydrocarbons (PAHs) and systematic review. The board endorsed NTP’s multi-year PAH research concept with some minor tweaks, and accepted a working group report on systematic review.

## Polycyclic aromatic hydrocarbons

Scott Masten, Ph.D., who heads the NTP Office of Nominations and Selection, provided a brief introduction to the [research concept on PAHs](#). Masten explained that an NTP concept represents a high-level look at the scope, approach, strategy, and direction that NTP would take in an area of interest, but is not to be thought of as a study design.

NTP toxicologist Cynthia Rider, Ph.D., lead for the PAH research effort, provided details about PAHs and the NTP approach to studying them. She said that PAHs are a large class of compounds found virtually everywhere in our environment. They occur naturally in petroleum and coal, or are created and released into the environment through natural events, such as forest fires and volcanoes. Rider noted that the 2010 Deepwater Horizon oil spill also reignited public concern over the human and ecological health hazards of PAHs.

## A flexible iterative process

“PAHs always occur in complex mixtures. There are at least 1,500 different PAHs, and there are numerous ways that humans can be exposed, including through food, inhalation, or through the skin,” Rider explained. NTP plans to look at a variety of health effects, using a battery of toxicity tests, including experimental animals and cell culture systems.

Rider discussed the pros and cons of two different approaches for assessing cumulative effects of PAHs — the component-based, or relative potency factor approach, and the whole mixture approach. She said the NTP proposal would contribute data to both approaches, and that they would be flexible and iterative. “The testing program will be built in units, with each round of testing informing the next,” Rider explained.



*Left to right, Birnbaum, Bucher, Eastmond, and Mary Wolfe, Ph.D., director of the NTP Office of Liaison Policy and Review, listened carefully to public comments and board discussions on high profile topics. (Photo courtesy of Steve McCaw)*



*Masten, who oversees the nomination and selection process for NTP studies, shared information about how the PAH research concept came to fruition. (Photo courtesy of Steve McCaw)*

## Using PAHs to move mixtures research forward

NTP plans to test both individual PAHs and complex environmental mixtures. Understanding how combined environmental exposures affect disease pathogenesis, or development, is a high priority for NIEHS and NTP. It is identified as Goal 4 in the [NIEHS strategic plan](#) and was the subject of a [workshop](#) in 2011.

Board members provided suggestions for moving the research forward, to ensure NTP looks at the breadth of endpoints or health effects PAHs may be causing, including endpoints relevant to known human effects.

“The board is supportive of the NTP’s efforts to help us better understand the health effects from PAHs. This effort will also help move the whole field of mixture science forward,” said BSC chair David Eastmond, Ph.D., of the University of California, Berkeley.

Board member Robert Chapin, Ph.D., of Pfizer, whole-heartedly agreed. “The NTP needs to be doing this. It needs to take on mixture science and wrestle it to the ground,” he said.

## Systematic review process

Most of the afternoon was spent discussing the [NTP approach](#) for systematic review that is being led by the NTP Office of Health Assessment and Translation ([OHAT](#)). Systematic review allows for more transparency of how NTP health assessment conclusions are determined ([see story](#)).

The board members listened to three public comments by phone and received all written [public comments](#).

Both NTP Associate Director John Bucher, Ph.D., and Eastmond reminded the board that its charge was to accept or reject the NTP BSC [draft working group report](#) on the approach to systematic review. The board unanimously accepted the report (see text box).

Andrew Rooney, Ph.D., and Kris Thayer, Ph.D., of OHAT took turns walking the board through the draft approach, answering questions, and talking about next steps, including developing several case studies to show how the process works.

## Evaluating NTP’s approach to reaching conclusions for literature-based evidence assessments

Lynn Goldman, M.D., of George Washington University, served as the NTP BSC working group chair, and summarized the draft report to the board.

The report on evaluating NTP’s approach for reaching conclusions for literature-based evidence assessments was developed by ten scientists representing academia, industry, and government. The draft provides comments and recommendations on each of the seven steps proposed for conducting the literature-based assessments.

“Overall, we felt the NTP’s proposed approach for reaching conclusions for literature-based assessments was very proactive in increasing transparency,” Goldman said.

In response to Goldman’s comment, NIEHS/NTP Director Linda Birnbaum, Ph.D., underscored NTP’s interest in getting public input. “There will be at least six opportunities for the public to comment, as we are conducting a systematic review,” she said. “We want to be transparent and we want to have stakeholders involved.”



*Rider, who is relatively new to NTP, shared her extensive knowledge about PAHs with the board. (Photo courtesy of Steve McCaw)*





*OHAT Deputy Rooney, left, and OHAT Director Thayer, reviewed their slides on the systematic review process, before presenting to board members. (Photo courtesy of Steve McCaw)*



*BSC Working Group Chair Goldman summarized the draft report on evaluating NTP's approach for reaching conclusions for literature-based evidence assessments. (Photo courtesy of Steve McCaw)*



*Birnbaum, left, took a few minutes during a busy BSC meeting to show appreciation to board members whose appointments ended on December 27, 2012. Birnbaum thanked Eastmond, above, for his service, especially his role as chair: Eastmond, Judith Zelikoff, Ph.D., of New York University Langone Medical Center; Elaine Faustman, Ph.D., of the University of Washington, and Dana Loomis, Ph.D., from the University of Nebraska Medical Center; all completed their appointments in December. Faustman and Loomis were unable to attend the meeting in person. (Photo courtesy of Steve McCaw)*



*Birnbaum and Zelikoff share a smile, after Birnbaum presented her with a certificate of appreciation. (Photo courtesy of Steve McCaw)*

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)

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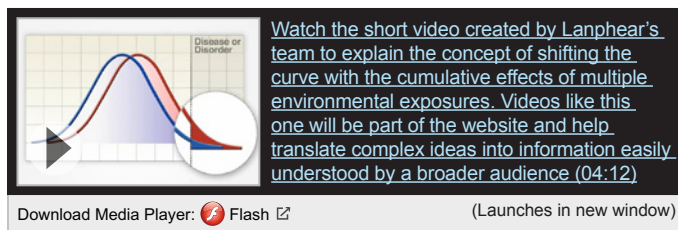
# Environmental health atlas provides interactive portal to promote awareness

By Ashley Godfrey

Longtime grantee [Bruce Lanphear, M.D.](#), gave an audience at NIEHS a sneak peek at the Canadian Environmental Health Atlas [website](#) he and his colleagues are developing.

In the presentation Dec 10, 2012, hosted by NIEHS/ NTP Director Linda Birnbaum, Ph.D., Lanphear described how his interactive document aims to raise awareness of the environment in health promotion and disease prevention, by making it easier to access the vast amounts of environmental health data the atlas integrates through its portal. He described the website as a work in progress, and sought both advice and input about it from the NIEHS community.

Lanphear is a professor at the Child and Family Research Institute in Vancouver, British Columbia. Lanphear, who is well known for his research on lead exposure and children's health, said he hopes the atlas will attract a broader audience and raise awareness that the environment is an essential part of any effort to promote human health. "Who is out there selling environmental health?" asked Lanphear, as he pointed to the relatively small number of relevant, user-friendly resources currently available. "Not enough people know that the environment is key [to public health]."



## Bringing life to a flat concept

Lanphear explained how the idea for the atlas emerged from an advisory panel and began as a paper book, but evolved into the current website. He and his team envision the website working as a portal or moderated wiki page, where knowledge can be easily accessed and translated for a general audience.



*Following his talk, Lanphear also made time to meet with Epidemiology Branch fellows. He told them about his struggle to make the scientific community realize that small amounts of lead exposure can have health effects, as small amounts were originally thought to be safe. (Photo courtesy of Steve McCaw)*



*Members of the Epidemiology Branch and NTP enjoyed Lanphear's lighthearted description of some of the struggles he encountered while creating the atlas. Shown, left to right, are Hazel Nichols, Ph.D., Dale Sandler, Ph.D., Mary Wolfe, Ph.D., and Abee Boyles, Ph.D. (Photo courtesy of Steve McCaw)*



By creating accurate but simple texts and graphics, Lanphear's goal is for the atlas to become an active, living document. He and his collaborators have worked to create a website that is about 50 percent text, with several interactive maps and other graphics. Plans are to incorporate infographics, by creating representations that display complex information and encourage readers to interact as they navigate. To help explain key concepts, the team plans to use videos to break down these concepts into simple examples that can be easily understood.

Narrative and case studies will also be a part of the atlas, Lanphear said, in response to a suggestion from NIEHS epidemiologist Allen Wilcox, Ph.D. Lanphear agreed that people respond to a story, and noted that the key to a successful website is to use graphics and videos that make complex data and concepts easy to follow.

"The challenge is to making it data accessible to a broader audience, without jeopardizing accuracy," stated Lanphear.

### Future goals

The website will be open to the public in 2013, but Lanphear's plans extend beyond the launch of the Canadian health atlas. He wants to expand this concept into a world atlas of environmental health, providing access to collective data from all around the world. By doing this, Lanphear expects to see additional patterns emerging, graphically, to underscore the role research plays in linking the environment with public health.

There are also plans to expand the current version of the atlas to include embedded analytic software, giving users the ability to both access and analyze publicly available data sets. Lanphear said he would like to contract with science writers to help fill in some of the gaps. Currently, sections of the atlas on asbestos and lead exposure are nearly complete, but Lanphear hopes to provide more data, by adding many other chemicals and exposures.

One of the most important goals for the atlas is to help people link evidence of environmental exposures with disease or, conversely, link a specific disease with evidence that may exist for potential environmental influences. Not only will this type of data be useful for the public audience, but it also speaks to researchers and trainees working at the intersection of the environment and human health. Lanphear pointed out that his model could be applied to several of the goals in the new NIEHS strategic plan, by filling the niche of translational knowledge through data accessibility.



*Members of the NIEHS intramural and extramural community, as well as staff from the NIEHS journal Environmental Health Perspectives, were on hand to hear about Lanphear's exciting concept. Shown, right to left, are Martha Dimes, Ph.D., Jane Hoppin, Sc.D., Dan Shaughnessy, Ph.D., and Kimberley McAllister, Ph.D. (Photo courtesy of Steve McCaw)*



*Living every presenter's worst nightmare, Lanphear was unable to navigate through the website during his presentation as he had planned. Staying quite calm and collected throughout, he reached out to his brother, who is part of his team working to complete the site, to ask for assistance, hoping he might be able to restore functionality. (Photo courtesy of Steve McCaw)*



## The Spatial Distribution of Health Hazards

The patterns of death and disease in Canada has less to do with advances in clinical medicine, biotechnology or pharmaceuticals than with our social and physical environment. Over the past 50 years, we have relied on medicine for our concerns about health and disease, investing tremendous resources in biotechnology and drugs. Access to health care services is a key determinant of health and the provision of health care services is essential, but the greatest burden of premature death, disease and disability is largely due to the conditions in which we live. Sixty percent of premature deaths are attributable to behavioural patterns, social circumstances and environmental exposures; only 10% are attributed to medical care.



*The atlas webpage gives a color-coded snapshot of Canadian environmental exposures and disease occurrences. The interactive site will be easy to navigate, with redundancy built in, along with separate sections on different exposures. (Screen shot courtesy of Bruce Lanphear)*

(Ashley Godfrey, Ph.D., is a postdoctoral fellow in the Molecular and Genetic Epidemiology Group in the NIEHS Laboratory of Molecular Carcinogenesis.)

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## Climate impacts of kerosene lamps used in developing countries

*By Jeffrey Stumpf*

While policy makers focus on carbon dioxide emissions when considering efforts to reduce climate change, a new study, funded in part by NIEHS, suggests that replacing the type of kerosene wick lamps used widely in developing countries would have a major impact in slowing the earth's warming trend.

The [report](#), presented by a multinational research coalition and published in the journal *Environmental Science and Technology*, adds the replacement of inefficient kerosene lamps to a list of practical changes that could help limit temperature increases over the next 50 years, while also dramatically improving indoor air quality.

Light produced by kerosene lamps is extremely important for the twenty percent of the world's population that lacks access to electricity. In fact, previous reports estimate that 77 billion liters of liquid fuel, mostly kerosene, are used annually to light houses without electricity. However, incomplete combustion of the lamp fuel often yields black carbon that absorbs light, thereby heating the atmosphere.

## Emission of significant amounts of black carbon

The study presents new laboratory and field measurements showing that 7–9 percent of kerosene consumed by this type of wick lamp is converted to carbonaceous particulate matter that is nearly pure black carbon. In contrast, less than half of 1 percent of emissions from wood combustion is black carbon. The authors note that 3 percent of global black carbon emissions come from these inefficient kerosene lamps.

One of the authors, [Kirk R. Smith, Ph.D.](#), is excited about simple opportunities to radically reduce the global footprint of human activities. “There are no magic bullets that will solve all of our greenhouse gas problems, but replacing kerosene lamps is low-hanging fruit,” said Smith, an NIEHS grantee and director of the Global Health and Environment Program at the University of California (UC), Berkeley, in a Nov. 28, 2012 [press release](#). “We don’t have many examples of that in the climate world.”

“There’s a lot of interest right now in reducing black carbon as a quick way to reduce climate warming — a way to reduce warming in the immediate future, although not a full solution to long-term climate change,” explained senior study author [Tami Bond, Ph.D.](#), a professor of civil and environmental engineering at the University of Illinois at Urbana Champaign.

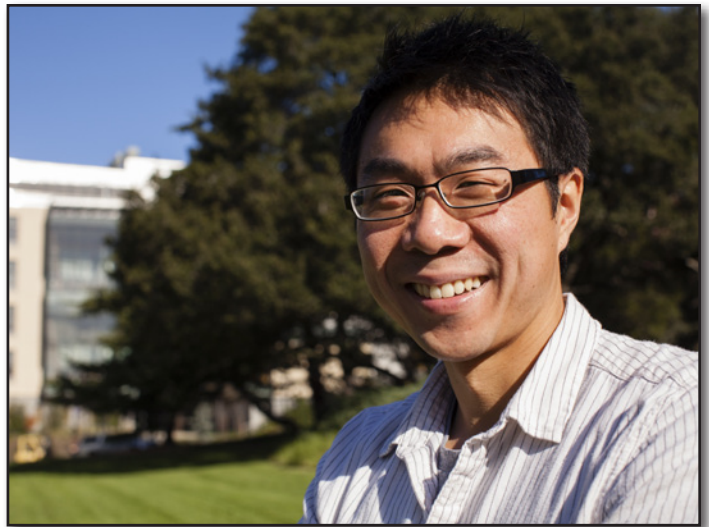
The report cited several examples of viable alternatives to kerosene lamps in addition to providing reliable and affordable electricity to households. Options include cheap light-emitting diode lamps or even simply more efficient kerosene-fueled lamps.

“There are many inexpensive, cleaner alternatives to kerosene lamps that are available now, and few if any barriers to switching to them,” Smith remarked.

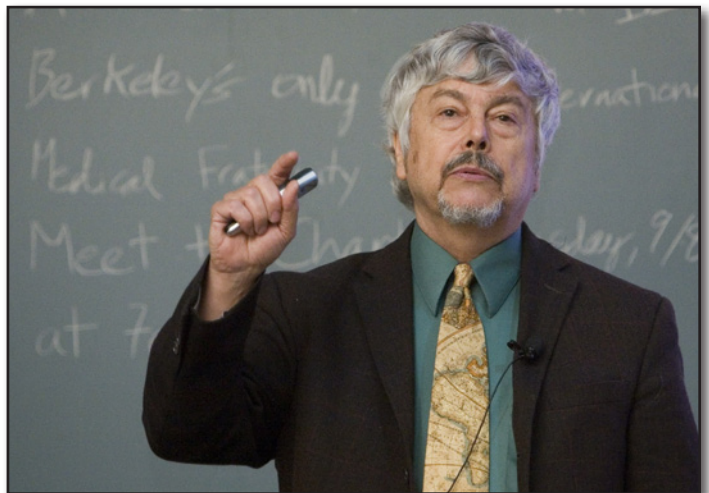
## Burning kerosene as an environmental health hazard

In poor households in developing countries, people live with and inhale the smoke generated from cooking and heating fires. The most recent estimates, which are part of the [Global Burden of Disease Study 2010](#) published Dec. 13, 2012, indicate that approximately four million people die prematurely each year from illness attributable to household air pollution due to biomass and coal cooking fuels alone.

[Work](#) funded by NIEHS and others, however, is starting to show that kerosene smoke whether from stoves or lamps is an additional important cause of ill health in these poor households. NIEHS has also funded a large new study by Smith and colleagues just starting in Nepal to examine the tuberculosis risks of kerosene smoke in much more detail.



*In addition to research on indoor air pollution and emissions associated with household energy in developing countries, Lam has worked on development of field respirators for wild land firefighters and investigations into the effects of ambient air pollution on lead paint degradation as a source of lead exposure in children. (Photo courtesy of Ajay Pillarisetti)*



*As a champion for reducing global climate change and promoting environmental health, Smith shared the 2007 Nobel Peace Prize and earned the 2009 Heinz Prize and 2012 Tyler Prize for achievements in environmental research. Smith has conducted pioneering studies of the health effects of indoor air pollution in homes that use inefficient cookstoves. (Photo courtesy of UC Berkeley)*



Replacing kerosene lamps is thus important not only for reducing global climate change but also decreasing the risk of adverse health outcomes.

“Getting rid of kerosene lamps may seem like a small inconsequential step to take, but when considering the collective impact of hundreds of millions of households, it’s a simple move that affects the planet,” said first author and UC Berkeley graduate student Nicholas Lam.

*Citations:* [Lam NL, Chen Y, Weyant C, Venkataraman C, Sadavarte P, Johnson MA, Smith KR, Brem BT, Arineitwe J, Ellis JE, Bond TC. 2012. Household light makes global heat: high black carbon emissions from kerosene wick lamps. Environ Sci Technol 46\(24\):13531-13538.](#)

[Pokhrel AK, Bates MN, Verma SC, Joshi HS, Sreeramareddy CT, Smith KR. 2010. Tuberculosis and indoor biomass and kerosene use in Nepal: a case-control study. Environ Health Perspect 118\(4\): 558-564.](#)

(Jeffrey Stumpf, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group.)

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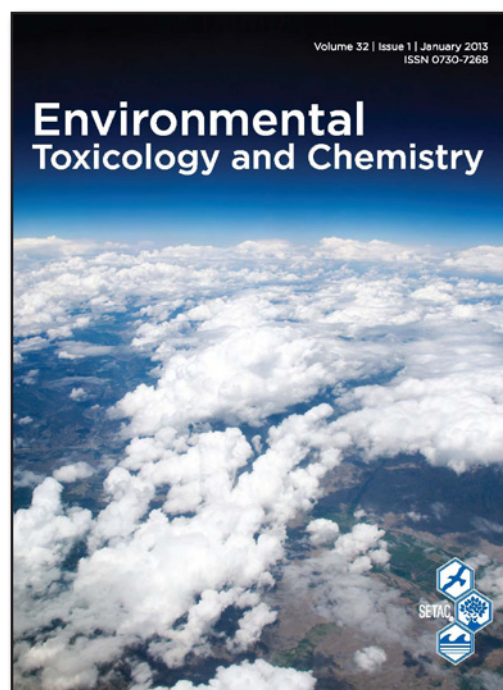
*Smoke emitted by simple wick lamps, similar to the one shown here, was found to be a significant but previously overlooked source of global black carbon. These lamps are used by hundreds of millions of households, and can be replaced by cleaner, affordable alternatives. (Photo courtesy of Ajay Pillarisetti)*

## Papers explore chemical risk assessment in light of climate change

*By Ed Kang*

A new series of papers, by leading experts in ecology, toxicology, and public health, explores the issues surrounding chemical risk assessment and management, in light of a changing global climate. Published online Dec. 18, 2012, the papers appear in the January 2013 issue of the journal [Environmental Toxicology and Chemistry \(ET&C\)](#). The seven publications detail the ways climate change might affect how chemicals are transported and cause toxicity to ecosystems and humans, and consequently how chemical risk assessment and management practices may have to be adapted.

“Risk assessors and public health practitioners need to understand how climate change may alter chemical risks to people in the future,” said one of the papers’ lead authors John Balbus, M.D., who is leading the NIEHS Global Environmental Health and Sustainable Development projects. “Existing data sources and assumptions used in exposure and risk assessment may not apply. Environmental health researchers and risk assessors will need to consider interactions between climate-related stressors and chemical stressors and other ways that future risks may be changing,” he added.





In their report, Balbus and his co-authors detail four broad groups of chemicals — natural toxins, pesticides, air pollutants, and legacy contaminants, such as dioxins, PCBs, and mercury — to illustrate the impact of climate change on the likelihood and severity of chemical insults to human health.

The authors call for research to inform how chemical use may change in the future; improved data sets and models to determine human exposure; focus on understanding how climate, weather, and human sensitivity interact; and refinement of regulatory models to utilize updated risk assessment and chemical management programs. They underscore that future projections of chemical risks will also need to explore how factors, including heat stress, psychosocial factors, urbanization, demographic shifts, and technology development, can potentially impact exposure, human susceptibility, and risk.

The authors conclude, “The potential cumulative impacts of multiple influences could significantly alter risks to human health. These alterations in risks have implications for national and international decision-makers involved in the regulation and authorization of chemical products.”



*Balbus has taken the lead in NIEHS global health initiatives, including participation in the Global Alliance for Clean Cookstoves. (Photo courtesy of Steve McCaw)*

### **The following publications in this series can be located on the [ET&C website](#):**

Balbus JM, Boxall AB, Fenske RA, McKone TE, Zeise L. 2013. Implications of Global Climate Change for the Assessment and Management of Human Health Risks of Chemicals in the Natural Environment. *Environ Toxicol Chem* 32(1):62-78.

Gouin T, Armitage JM, Cousins IT, Muir DC, Ng CA, Reid L, Tao S. 2013. Influence of Global Climate Change on Chemical Fate and Bioaccumulation: The Role of Multimedia Models. *Environ Toxicol Chem* 32(1):20-31.

Hooper MJ, Ankley GT, Cristol DA, Maryoung LA, Noyes PD, Pinkerton KE. 2013. Interactions Between Chemical and Climate Stressors: A Role for Mechanistic Toxicology in Assessing Climate Change Risks. *Environ Toxicol Chem* 32(1):32-48.

Landis WG, Durda JL, Brooks ML, Chapman PM, Menzie CA, Stahl RG, Stauber JL. 2013. Ecological Risk Assessment in the Context of Global Climate Change. *Environ Toxicol Chem* 32(1):79-92.

Moe SJ, De Schamphelaere K, Clements WH, Sorensen MT, Van den Brink PJ, Liess M. 2013. Combined and Interactive Effects of Global Climate Change and Toxicants on Populations and Communities. *Environ Toxicol Chem* 32(1):49-61.

Rohr JR, Johnson P, Hickey CW, Helm RC, Fritz A, Brasfield S. 2013. Implications of Global Climate Change for Natural Resource Damage Assessment, Restoration, and Rehabilitation. *Environ Toxicol Chem* 32(1):93-101.

Stahl RG, Hooper MJ, Balbus JM, Clements W, Fritz A, Gouin T, Helm R, Hickey C, Landis W, Moe SJ. 2013. The Influence of Global Climate Change on the Scientific Foundations and Applications of Environmental Toxicology and Chemistry: Introduction to a SETAC International Workshop. *Environ Toxicol Chem* 32(1):13-19.

The series of seven papers stems from a [Society of Environmental Toxicology and Chemistry \(SETAC\)](#) international workshop held in July 2011 and sponsored by NIEHS and the NIEHS Superfund Research Program. In an editorial accompanying the release of the publications, ET&C Editor-in-Chief Allen Burton, Ph.D., notes, “This collection of peer-reviewed papers represents the consensus of expert participants from across academia, government, and business.”

“The papers tackle the impacts of global climate change on chemical contaminants, organism acclimation, and vulnerable communities, as important considerations for future assessments of human and ecological risk,” the editorial states.

(Ed Kang is a public affairs specialist in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)

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## Basic metabolism studies lead to a treatment for laminitis in horses

*By Sara Mishamandani*

Hulahalla, a 4-year-old thoroughbred horse, was lame and a day away from being euthanized when University of California (UC), Davis veterinarian Alonso Guedes, D.V.M., Ph.D., made a call to UC Davis researcher Bruce Hammock, Ph.D. Guedes was interested in a compound that had been developed through NIEHS-funded Superfund Research Program (SRP) basic research. Testing in animal studies had demonstrated the safety of the compound, as well as its potential for inhibiting inflammation.

Within hours after Guedes administered the experimental drug, Hulahalla was back on her feet, the first sign she was recovering from laminitis, an agonizingly painful and usually terminal foot disease often seen in horses.

Today, one year after treatment, Hulahalla remains an active and healthy companion animal, and her example is inspiring continuing efforts to improve outcomes for other animals with laminitis.

Researchers at the UC Davis SRP, led by Hammock, had originally developed the compound to study basic catalytic mechanisms of an enzyme in the body and, in the process, found that the compound also relieved neuropathic pain and inflammation ([see text box](#)).

### Making the call for treatment

The opportunity for the Hammock group to test the anti-inflammatory drug on larger animals presented itself through Guedes, who had been collaborating with the Hammock lab for several years. Laminitis is initiated by inflammation, progresses into severe inflammatory pain, and then into a chronic or neuropathic pain condition that leads to tissue destruction and often causes severe high blood pressure.



*Guedes, pictured with Hulahalla, is a veterinarian at UC Davis with a research focus in pain biology and analgesic pharmacology. (Photo courtesy of UC Davis)*

“In the United States, it is estimated that laminitis will strike 15 percent of horses during their lifetimes, and 75 percent of horses with laminitis will lose their lives,” said Guedes.

Hulahalla developed acute laminitis in both front feet. Veterinarians at UC Davis treated her with the standard of care for several days, but her condition deteriorated and she refused to stand. Guedes made an emergency call to Hammock, after obtaining compassionate permission to use the soluble epoxide hydrolases (sEH) inhibitor they had developed — the only option left, aside from euthanasia, to relieve the extreme pain and suffering.

Within three hours after clinicians administered the drug to Hulahalla, she was able to stand. Her pain level and blood pressure decreased progressively and, after three days, she could walk almost normally and her systolic blood pressure dropped significantly, from 200 to 110. After five days, Hulahalla was doing very well and no longer needed the sEH inhibitor. There has been no reoccurrence of laminitis or sign of adverse drug effects.

Bora Inceoglu, Ph.D., a collaborator of Guedes and Hammock, is working to move the compounds to the clinic for human diabetic and other neuropathic pain. “It is often hard to extrapolate from treatment of rodent models of pain to man,” said Inceoglu. This mare was suffering from a real disease. Not only is it gratifying to save the life of Hulahalla, but she and other horses provide strong evidence that our success with treating neuropathic pain in rodents can be extrapolated to man.”

### **Moving the treatment forward**

Since testing the compound with Hulahalla in 2011, four additional horses suffering from laminitis have been treated under a compassionate use protocol approved by

## **Starting from basic NIEHS research**

Since its inception 25 years ago, SRP has supported the Hammock lab to study the role of epoxide hydrolases, enzymes that catalyze the opening of epoxide rings, to detoxify a variety of environmental chemicals.

Some epoxides are very reactive chemical compounds that form inside the body during the metabolism of drugs and environmental contaminants. Because of their reactivity, such epoxides can be potent mutagens, toxins, and carcinogens. Thus epoxide hydrolases offer significant protection against cellular injury, by transforming these harmful epoxides into less toxic and more water soluble compounds.

NIEHS-funded researchers led by Hammock discovered another soluble epoxide hydrolase (sEH), a new form of the enzyme that exists in the cell cytosol and degrades chemically stable fatty acid epoxides. To investigate the biological role of this enzyme, they created potent inhibitors. Inhibitors are commonly used to determine the location of the enzyme’s active site and to study factors that control enzyme activity.

Hammock and his team discovered that sEH is very good at converting fatty acid epoxides into diols, eliminating the epoxides from the body. However, some fatty acid epoxides of omega-3 and omega-6 can be very beneficial and have been found to reduce inflammation, inflammatory pain and, surprisingly, even chronic or neuropathic pain. They found that the potent inhibitors that they created to study sEH could be used in mouse and rat models as a drug to reduce inflammation and inflammatory pain more effectively than non-steroidal anti-inflammatory drugs (NSAIDs). They also began studying the use of the drug with horse enzymes, but had not yet used the drug in a horse or any other companion animal.

“It is very hard to tell where science will lead,” says Hammock. “We are hoping that the fundamental work supported by NIEHS on foreign compound metabolism will result in a treatment for devastating pain and inflammation in dogs and cats, as well as horses.”

A clinical trial to assess the drug’s safety and establish a tolerable dose for the compound is expected to begin in the spring. Further clinical trials would be needed to establish the drug’s effectiveness as a laminitis treatment.



the UC Davis Institutional Animal Care and Use Committee. That protocol allows animals to be treated with an experimental drug if no approved alternative treatment exists. Hulahalla experienced a complete remission that has lasted for more than a year, and three others have shown some improvement.

“The soluble epoxide hydrolase inhibitors are far more effective than any other commercial compound we have tried with pain models,” said former SRP graduate student Karen Warren, Ph.D.

“This is an unusual step for us to announce this so far in advance, but because euthanasia is often the only way to alleviate pain in severe laminitis, we felt that it was important to let the veterinarians and horse owners know that this compound has shown potential as a treatment,” said Guedes.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)



*Hammock's research interests range across omics platform development, pest control, and drug development. He has been honored for his teaching and mentoring, as well as for his groundbreaking scientific research. (Photo courtesy of Bruce Hammock)*



*Laminitis made it too painful for Hulahalla to stand. In this 2011 photo, she is wearing a pair of equine gel orthotic comfort boots on her front hooves, a common veterinary treatment to help ease pain in cases of wounds, drains, casts, and other special conditions. (Photo courtesy of Robert Warren)*



*Hulahalla a year later, showing the effects of the treatment were dramatic. (Photo courtesy of Robert Warren)*

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# Uranium exposure linked to increased lupus rate

*By Amanda Harper*

People living near a former uranium ore processing facility in Ohio are experiencing a higher than average rate of lupus, according to a new NIEHS-funded study conducted by scientists at the University of Cincinnati (UC) and Cincinnati Children's Hospital Medical Center.

Systemic lupus erythematosus, or lupus, is a chronic inflammatory disease that can affect the skin, joints, kidneys, lungs, nervous system, and other organs of the body. The underlying causes of lupus are unknown, but it is much more common in women.

For this new study, a collaborative team of UC and Cincinnati Children's researchers compared lupus rates in people who were exposed to uranium to rates in those who were not, in an effort to explain the high number of lupus cases reported in a suburban Cincinnati community.



*Lead researcher Lu is shown outside Cincinnati Children's Hospital Medical Center (CCHMC). (Photo courtesy of CCHMC)*

## Environmental exposures from a former uranium processing plant

In their extensive review of medical records and serum antibody analysis, to verify the cases, the researchers found that people who were exposed to higher levels of uranium, based on their living in close proximity to a former uranium ore processing plant, had lupus rates four times higher than the average population.

“Former studies have suggested that people with lupus may be more sensitive to radiation, and that both genetics and environmental exposures play a role in disease development,” said Pai-Yue Lu, M.D., a pediatric rheumatology fellow at Cincinnati Children's and lead researcher for the study. “Our study shows a strong correlation between exposure to uranium, a radioactive substance, and an increased lupus rate that merits further investigation.”

“With more research in this area, we may gain additional insight on the types of environmental factors that contribute to lupus development and the mechanisms by which they work,” Lu added. “There could be other effects of uranium and related exposures that could contribute to or help explain our findings.”

Lu presented this finding and its potential implications in November 2012 at the American College of Rheumatology annual meeting in Washington, D.C. She completed the project as part of her master's degrees in [clinical and translational research training](#) at UC.



*Senior author Pinney also serves as a member of the Fernald Medical Monitoring Program staff. (Photo courtesy of CCHMC)*



The Cincinnati-based team's research is based on nearly two decades of data collected through the [Fernald Medical Monitoring Program](#), the first and largest legally mandated comprehensive medical monitoring program in the U.S. The program was established in 1990, after a federal investigation revealed that National Lead of Ohio's Feed Materials Production Center in the Hamilton County, Ohio, community of Fernald, was emitting dangerous levels of uranium dust and gases into surrounding communities.

"The availability of this cohort, and carefully collected data and biospecimens, provides a great setting to ask research questions," said [Susan Pinney, Ph.D.](#), UC professor of environmental health and principal investigator on the Fernald study.

Almost 10,000 community residents enrolled in the Fernald Medical Monitoring Program. Community residents were classified into several exposure groups — high exposure, moderate exposure, low exposure, and no exposure. Uranium plant workers were not part of this study, since the focus of the study was environmental rather than occupational exposure.

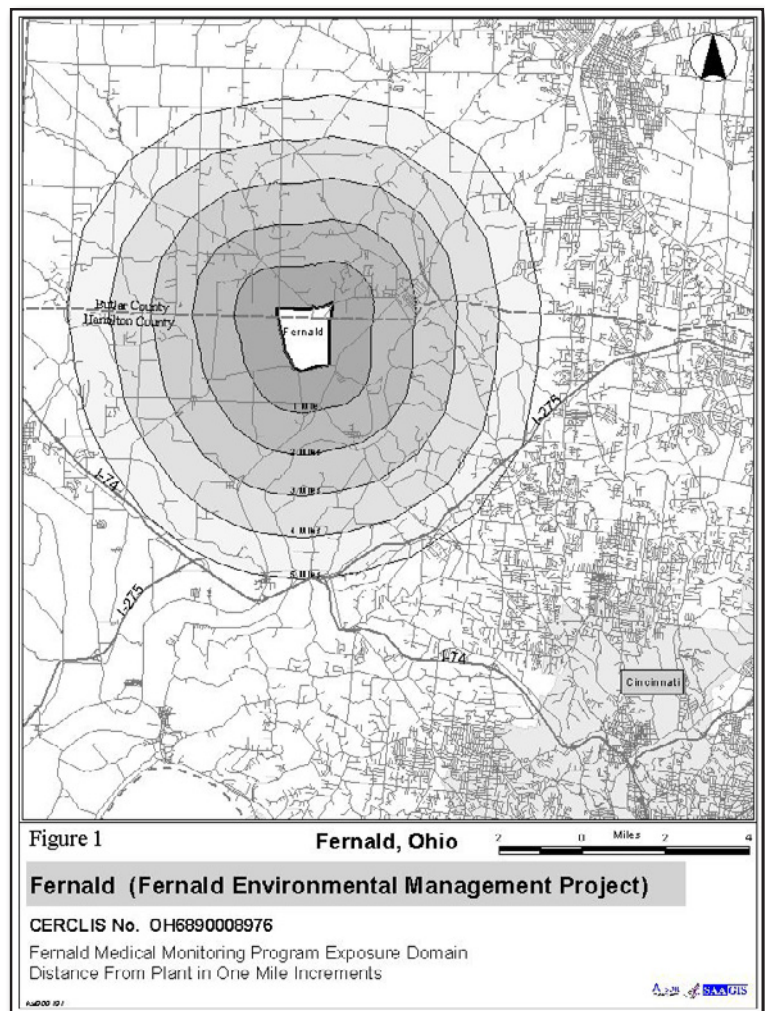
"Typical U.S. incidence rates for lupus are 1.8 to 7.6 cases per 100,000. Among the 25 confirmed lupus cases we identified through the Fernald community cohort, 12 were in the high exposure group, eight experienced moderate exposure, and five were in the low exposure group," Lu explained.

Research was supported by a pilot grant from the [Center for Environmental Genetics \(CEG\)](#), an NIEHS-funded program to support core facilities and technologies needed to conduct innovative research that focuses on how environmental agents interact with genetic and epigenetic factors to influence disease risk and outcome. [Shuk-mei Ho, Ph.D.](#), the Jacob A. Schmidlapp Endowed Chair and professor in the UC Department of Environmental Health, serves as director of the CEG.

*Citation:* Lu P-Y, Kottyan LC, Pinney SM, James JA, Xie C, Buckholz JM, Harley JB. 2012. Identifying a Link Between Uranium Exposure and Systemic Lupus Erythematosus in a Community Living near a Uranium Plant. [Arthritis Rheum](#) 64:(10Suppl):S686.

(Amanda Harper is a public information officer in the Office of Public Relations and Communications at the UC Academic Health Center. For more information about this study, contact Harper by phone at 513-558-4657 or by email at [amanda.harper@uc.edu](mailto:amanda.harper@uc.edu))

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*This map shows the one-mile increments that defined uranium exposure levels for subjects in the study of residents of Fernald, located just outside Cincinnati. (Map courtesy of the Fernald Environmental Management Project)*



# NICEATM holds workshop on new safety tests for pertussis vaccines

*By Debbie McCarley and Cathy Sprankle*

NIEHS and U.S. Food and Drug Administration (FDA) scientists joined other experts from around the world at a workshop to consider improved methods and approaches for safety testing of vaccines that protect against pertussis. The “International [Workshop](#) on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward” was held Nov. 28-29, 2012, at the William H. Natcher Conference Center on the NIH campus in Bethesda, Md.

The workshop provided a forum for participants to review protocols and available data from an ongoing international study of *in vitro* alternatives for safety testing of pertussis vaccines. The workshop participants also considered the next steps to achieve validation, global acceptance, and implementation of these test methods.

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods ([NICEATM](#)) organized the workshop in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods ([ICCVAM](#)) and partner organizations of the [International Cooperation on Alternative Test Methods](#).

## Pertussis is an important public health concern

Pertussis, also known as whooping cough, is a highly contagious bacterial disease that was once a major cause of childhood mortality. While widespread vaccination has substantially decreased the incidence of pertussis, recent outbreaks have led public health officials to recommend renewed and expanded vaccination efforts.

The HIST is a key safety test performed on pertussis vaccines, to prevent adverse effects from residual pertussis toxin that has not been completely inactivated. However, the testing uses a large number of animals, and many of the animals experience pain and distress. Therefore, NICEATM and ICCVAM identified the HIST as a priority for future research, development, and validation of alternative test methods that could reduce, refine, or replace animal use for pertussis vaccine safety testing.

Given the need for alternatives to the HIST, an international committee of regulatory and industry experts was established to evaluate animal replacement methods that could also provide greater accuracy, precision, and efficiency. The committee initiated an international collaborative study on *in vitro* alternatives to the HIST. In this study, reference pertussis toxin and seven acellular pertussis vaccines from three manufacturers were distributed to 12 international laboratories for testing. Data were generated on the detection of pertussis toxin in toxin-spiked vaccines using conventional high-performance liquid chromatography and enzyme-linked immunosorbent assay platforms, as well as advanced cell-based and genomics technologies.

Workshop participants reviewed data from this study. Based on the findings, attendees selected two of the cell-based methods for further development and optimization in the next international collaborative study planned for later this year.

“Both vaccine manufacturers and regulators are actively working to develop and validate improved alternatives that can achieve acceptance and use,” noted William Stokes, D.V.M., who participated in the workshop in his role as director of NICEATM. “This is an important opportunity to reduce animal use and improve safety testing with a test that has a clear impact on public health.”

A more detailed summary of the workshop and speaker presentations are available on the [ICCVAM website](#). A report on the workshop will appear later this year in the journal *Biologicals*.



*Stokes, front right, joined more than 40 scientists from 11 countries representing vaccine manufacturers and government regulatory agencies at the November 2012 workshop. (Photo courtesy of NICEATM)*

(Debbie McCarley is a special assistant to Stokes. Cathy Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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## Casey meets with international experts to assess endocrine disruptor testing

*By Debbie McCarley and Cathy Sprankle*

NTP scientist Warren Casey, Ph.D., participated in two expert meetings in November 2012 that considered *in vitro* methods for detecting substances that might interfere with normal hormone function. Casey is acting director of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods ([NICEATM](#)).

Casey attended the annual meeting of the Validation Management Group for Non-animal Testing (VMG-NA) Nov. 29-30. He also attended the first meeting of the Thyroid Scoping Effort Expert Group (TSEEG) Nov. 28. Both meetings were sponsored by the Organisation for Economic Co-operation and Development (OECD) and took place at OECD Headquarters in Paris.

NICEATM is committed to building global partnerships to advance alternatives to animal testing. Participation in events such as the recent OECD meetings is an important part of developing those partnerships.

### **Concerns about endocrine disruptors spur test method development**

Endocrine disruptors are substances that interfere with the normal function of hormones in the endocrine system. Studies have shown that animals exposed to these substances exhibit reproductive and developmental abnormalities. These studies have raised concerns that such substances might have similar effects in humans, and a growing body of research supports this hypothesis. Thus, test methods are needed that can provide accurate and timely identification of potential endocrine disruptors.

NICEATM coordinated an international validation study of the BG1 Luc estrogen receptor (ER) transactivation (TA) assays, which identify substances with the potential to induce or inhibit activity of the estrogen receptor. The BG1 Luc ER TA test methods gained international acceptance when the OECD adopted a test guideline describing them in October 2012.

The November VMG-NA meeting considered additional methods currently under evaluation for this purpose by the U.S. Environmental Protection Agency (EPA) and groups in Europe and Japan. Casey serves on the study management teams for these projects. He commented on their progress and addressed questions about selection of reference chemicals and evaluation methods.

Another topic considered at the November meeting was the development of medium and high throughput screening methods for endocrine disruptors. Casey presented recent work performed by the [Tox21](#) consortium on the adaptation of the BG1 Luc ER TA methods to a high throughput platform, which was one of several case studies discussed at the meeting.

### **Group established to evaluate status of thyroid assays**

Participants of the newly established TSEEG gathered in an effort to identify available assays for the detection of potential thyroid disruptors and assess their suitability for regulatory use or potential future test guideline development.

The thyroid gland regulates energy use in the body and affects the body's response to other hormones. It is another potential target of endocrine disruptors. In the past, the thyroid system has received less attention than the estrogen system, in regard to the development of test methods. Establishment of the TSEEG was recommended by the VMG-NA to address this important need. The expert group is chaired by Kevin Crofton, Ph.D., of the EPA National Center for Computational Toxicology.



*Casey is one of several scientists from NIEHS research divisions who are striving for a better understanding of endocrine disruption. (Photo courtesy of Steve McCaw)*



Recommendations from this meeting will be submitted to the national coordinators of the OECD Test Guidelines Programme, who will consider it at their meeting later this spring. Approval of the recommendations will provide direction for future development of test methods to identify potential thyroid disruptors.

(Debbie McCarley is a special assistant to William Stokes, D.V.M. Cathy Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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## This month in EHP

**Environmental Health Perspectives (EHP)** goes paperless in January with its first entirely electronic issue featuring a cover article on cooler-by-design architecture and engineering.



<http://twitter.com/ehponline>

### Alternatives to Air Conditioning for a Warm World

The developing world is home to most of the globe's hottest and fastest-growing cities as well as a rapidly expanding middle class that can now afford the amenities that citizens in the developed world have long taken for granted. High on that list is the air conditioner. Although air-conditioning use will certainly continue to increase globally with no serious regulatory frameworks in sight, some observers believe awareness of its environmental impact is beginning to change the ways in which architects and engineers, at least, are approaching the challenge of keeping people cool.



### Beyond Uncertainty Factors: Protecting the Tails of the Bell Curve

For decades, environmental risk assessors have tried to address interindividual variation by setting exposure limits low enough to protect the most sensitive subgroups in the population. Now they are looking for more targeted ways to address the underlying factors that govern individual susceptibility.

### Podcast: The Secret Life of Fat Tissue, with Michele La Merrill

Your bulges are busier than you may think. Many people see adipose tissue — fat — as nothing more than lumpy extra baggage. But fat serves several important functions in the body. It helps us store energy and endocrine hormones that can affect behavior, energy regulation, immunity, and vascular function — to name a few. It also protects against toxic effects of persistent organic pollutants, or POPs. In this [podcast](#), Michele La Merrill, Ph.D., talks with host Ashley Ahearn about the diverse ways that fat interacts with these chemicals as both a modulator and a target of POP toxicity.

Featured commentaries, reviews, and research this month include:

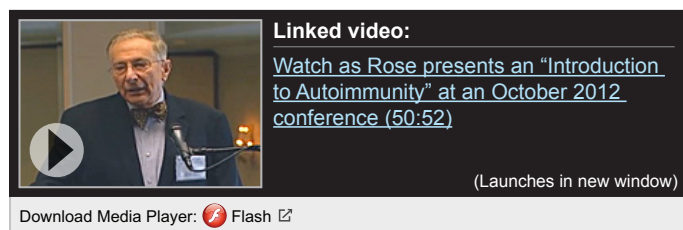
- Genetic Modification of the Association Between Peripubertal Dioxin Exposure and Pubertal Onset in a Cohort of Russian Boys
- Possible Positive Selection for an Arsenic-Protective Haplotype in Humans
- Coplanar Polychlorinated Biphenyls Impair Glucose Homeostasis in Lean C57BL/6 Mice and Mitigate Beneficial Effects of Weight Loss on Glucose Homeostasis in Obese Mice
- Climate Change and Older Americans: State of the Science

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## Rose to give distinguished lecture

*By Sheetal Thakur*

The first 2013 NIEHS distinguished lecture, “Myocarditis: an environmentally initiated autoimmune disease,” will be presented by Noel Rose, M.D., Ph.D., Jan. 8 at 11 a.m. in Rodbell Auditorium. Rose’s visit to NIEHS will be hosted by Dori Germolec, Ph.D., who is the Systems Toxicology Group leader in the NTP Toxicology Branch.



Rose is a professor of pathology, molecular microbiology, and immunology, as well as the director of the Autoimmune Disease Research Center at Johns Hopkins University (JHU). He is a pioneer and internationally renowned expert in the field of autoimmune diseases, and has served as the chair of the Autoimmune Diseases Coordinating Committee of the National Institutes of Health. In his early career during the 1950’s, Rose demonstrated, for the first time, that immunizing animals experimentally with their own thyroglobulin induces autoimmune thyroiditis. This finding revolutionized the outlook of the entire research community on autoimmune diseases.

The Rose laboratory at JHU continues to investigate the triggers, mechanisms, and pathology of autoimmune diseases, in both clinical and laboratory animal settings. His group’s research has unraveled the complex interplay between genetic and environmental factors that influence the development of autoimmune diseases. Some of the recent findings from Rose’s group highlight the significance of autoantibodies in the human population and their prediagnostic value in the early detection of autoimmune thyroid disease.



*Rose made his first seminal discovery about Hashimoto’s thyroiditis in 1956 — the beginning of a long series of important contributions toward the understanding of autoimmune diseases and the gene-environment interactions responsible for them. (Photo courtesy of Johns Hopkins University)*

In his career of 50-plus years, Rose has published more than 200 papers, edited 17 books, and given numerous lectures at conferences worldwide. His many awards include the 2005 American Society for Microbiology Founders Distinguished Service Award, 2006 Keystone Lifetime Achievement Award, and the 2009 Nicolaus Copernicus Medal from the Polish Academy of Sciences. Rose has dedicated his career to understanding the mechanisms and pathogenesis of autoimmune diseases and his research continues to enrich the field and suggest therapeutic strategies for these debilitating diseases.

(Sheetal Thakur, Ph.D., is an Intramural Research Training Award fellow in the NTP Toxicology Branch.)

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## Upcoming data integration workshop

*By Eddy Ball*

An innovative NIEHS-sponsored program continues its workshop series with an exploration of “[Integrating Environmental Health Data to Advance Discovery](#)” Jan. 10-11 at the Keck Center in Washington, D.C.



The workshop, which is part of the National Academies Emerging Science for Environmental Health Decisions series, is free and open to the public. [Registrations](#) for on-site attendance and webcast access are now being accepted.

### Integrating increasing volumes of data

Research in biomedical sciences has undergone a dramatic transformation in the past two decades. Science is increasingly data intensive, computational, interdisciplinary, and collaborative — a trend that is pervasive throughout science, and imposing new challenges for biomedical research.

While significant progress has been made in the development of digital technologies, community-wide principles, and resource management for some large and rapidly expanding data types, such as genomic sequences, the integration of existing heterogeneous data sets has lagged. This lag presents particular challenges for environmental health science, which is uniquely and inherently cross-disciplinary.

This meeting aims to foster discussion about the need for enhanced data integration in environmental health sciences and evaluate the lessons that can be learned from integrative initiatives in other scientific domains. It also offers participants a forum for strategizing about ways the community can take major steps toward improving data coordination and access to advance understanding about environmental effects on human health.

### An ongoing series of workshops

Sponsored by NIEHS, the program holds three workshops per year on the use of new discoveries, tools, and approaches for guiding environmental health decisions. The workshops provide a public venue for communication among government, industry, environmental groups, and the academic community.



The data integration workshop is the thirteenth in the [series](#), which began in July 2009 with a workshop on the “Use of Emerging Science and Technologies to Explore Epigenetic Mechanisms Underlying the Developmental Basis for Disease.” Past presentations are archived online, and videos are available for several recent workshops.

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## Extramural papers of the month

*By Nancy Lamontagne*

- [Mechanism for melanoma risk in people with red hair and fair skin](#)
- [Early exposures to air pollution linked with autism](#)
- [Flame retardant Firemaster 550 confirmed as endocrine disruptor](#)
- [Prenatal mercury and ADHD](#)



Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

## Mechanism for melanoma risk in people with red hair and fair skin

A study supported by the NIEHS identifies a new mechanism that helps explain risk for melanoma, the most dangerous type of skin cancer, and provides information that might aid in protecting people with the highest melanoma risk.

Pheomelanin, the predominant skin pigment for people with red hair and fair skin, is less protective against ultraviolet (UV) radiation damage than the eumelanin found in people with dark skin and hair. However, studies indicate that reduced UV protection may not fully explain why individuals with red hair and freckles are more at risk for melanoma, so the researchers conducted a study involving dark-colored mice with the typical gene variant for a predominance of eumelanin and mice with the variant that produces red hair and fair skin in humans.

Even without UV exposure, the red hair/fair skin mice had a greater number of invasive melanomas, suggesting that the pheomelanin pigment itself was involved in melanoma. The researchers then tested mice with no skin pigment (albino), and these mice developed fewer melanomas than the red hair/fair skin mice. In addition, the red hair/fair skin mice had significantly greater oxidative DNA and lipid damage than the albino mice. The study findings suggest that in the absence of UV exposure, the pheomelanin pigment contributes to melanoma via oxidative damage. The researchers say protection from ultraviolet radiation remains important, but additional strategies may be needed to achieve the best melanoma prevention.

*Citation:* Mitra D, Luo X, Morgan A, Wang J, Hoang MP, Lo J, Guerrero CR, Lennerz JK, Mihm MC, Wargo JA, Robinson KC, Devi SP, Vanover JC, D’Orazio JA, McMahon M, Bosenberg MW, Haigis KM, Haber DA, Wang Y, Fisher DE. 2012. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. *Nature* 491(7424):449-453.

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## Early exposures to air pollution linked with autism

NIEHS grantees report that exposure to local traffic-related air pollution and regional air pollution in the womb and during the first year of life is associated with increased risk for autism. The study builds on previous research in which the grantees found that children born to mothers who live within 309 meters of freeways had an increased risk of developing autism.

In the new study, the researchers examined data from children enrolled in the Childhood Autism Risks from Genetics and the Environment study, including 279 children with autism and 245 control children with normal development. They estimated traffic-related pollution exposures using the mother's address and used U.S. Environmental Protection Agency's Air Quality System measurements of regional pollution.

The children with autism were more likely than the control children to live in homes with the highest exposure to traffic-related air pollution during gestation (adjusted odds ratio [AOR] 1.98 [95 percent confidence interval (CI) 1.20-3.31]) and the first year of life (AOR, 3.10 [95 percent CI, 1.76-5.57]). During gestation, exposure to regional nitrogen dioxide and particulate matter less than 2.5 and 10 microns in diameter was also associated with autism. The researchers say that additional population and toxicological studies of likely biological pathways are needed to determine if the air pollution exposure causes the increase in autism risk.

*Citation:* Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. 2012. Traffic-Related Air Pollution, Particulate Matter, and Autism. Arch Gen Psychiatry; doi:10.1001/jamapsychiatry.2013.266 [Online 26 November 2012].

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## Flame retardant Firemaster 550 confirmed as endocrine disruptor

The flame-retardant mixture Firemaster 550 is commonly found in household dust, but the physiological effects of its components at relevant exposure levels aren't known. An animal study conducted by NIEHS grantees shows that perinatal exposure to the flame-retardant mixture is associated with endocrine disrupting effects. The researchers observed weight gain, early onset of puberty, and cardiovascular health effects at levels that are relevant to human exposure and lower than the no observable adverse effects level reported by the manufacturer.

The researchers evaluated the effects of FM 550 in rats exposed to 100 or 1000 micrograms of the flame-retardant per day during gestation and lactation. They found that the components of Firemaster 550 accumulated in tissues of exposed mice as well as their offspring and induced metabolic syndrome characteristics in the offspring. They observed higher levels of the thyroxine thyroid hormone and reduced hepatic carboxylesterase activity in the exposed mice. The offspring exhibited advanced female puberty, weight gain, male cardiac hypertrophy, and problems with exploratory behaviors. The researchers say that their findings reveal that the flame retardant may affect growth and neurodevelopment and support the need for more research into the mechanisms involved and human exposure levels.

*Citation:* Patisaul HB, Roberts SC, Mabrey N, McCaffrey KA, Gear RB, Braun J, Belcher SM, Stapleton HM. 2012. Accumulation and Endocrine Disrupting Effects of the Flame Retardant Mixture Firemaster(®) 550 in Rats: An Exploratory Assessment. J Biochem Mol Toxicol; doi: 10.1002/jbt.21439 [Online 8 November 2012].

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# Prenatal mercury and ADHD

A new paper from NIEHS-funded researchers found an association between low-level prenatal mercury exposure and increased risk of attention-deficit/hyperactivity disorder (ADHD)-related behaviors in children. However, consuming more than two serving of fish per week was linked with a lower risk for ADHD-related behaviors.

The researchers studied children born in New Bedford, Mass. They conducted neuropsychological assessments for children at age 8 who had peripartum maternal hair mercury measures (421 children) or maternal reporting of fish consumption during pregnancy (515 children). The mothers' median hair mercury level was 0.45 micrograms per gram ( $\mu\text{g/g}$ ) (range = 0.03 to 5.14  $\mu\text{g/g}$ ), and 52 percent of them consumed more than two servings of fish a week. Multivariable regression models showed that mercury exposure was associated with inattention and impulsivity/hyperactivity. Associations between mercury and behavior were detected primarily for boys. However, when the mothers consumed more than two servings of fish per week, there was a protective effect for ADHD-related behaviors, particularly impulsive/hyperactive behaviors (relative risk = 0.4; 95 percent CI 0.2-0.6).

The author of a related editorial said that the study's findings point to the need for a national scientific advisory panel to evaluate environmental influences of ADHD and that new evidence linking environmental contaminants with ADHD reinforces the urgency of revising the regulatory framework for environmental contaminants and toxicants.

*Citation:* [Sagiv SK, Thurston SW, Bellinger DC, Amarasiriwardena C, Korrick SA](#). 2012. Prenatal Exposure to Mercury and Fish Consumption During Pregnancy and Attention-Deficit/Hyperactivity Disorder-Related Behavior in Children. *Arch Pediatr Adolesc Med* 166(12):1123-1131.

*Related Editorial:* [Lanphear BP](#). 2012. Attention-Deficit/Hyperactivity Disorder: A Preventable Epidemic? *Arch Pediatr Adolesc Med* 166(12):1182-1184.

(Nancy Lamontagne is a science writer with MDB, Inc., a contractor for the NIEHS Division of Extramural Research and Training, Superfund Research Program, and Worker Education and Training Program.)

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## Intramural papers of the month

*By Sonika Patial, Bhargavi Rao, Darshini Trivedi, and Sheila Yong*

- Chloride channel regulation may lead to improvements in vascular disease
- Mechanisms of anticancer drug resistance
- New insights into lung dendritic cell migration in adaptive immune responses
- Tobacco smoke exposure *in utero* increases adult cardiovascular disease risk



## Chloride channel regulation may lead to improvements in vascular disease

A recent NIEHS-funded study determined that the migration of vascular smooth muscle cells (VSMCs) is regulated by chloride ion flux through chloride channel CIC-3. The team is the first to show that the chloride current dramatically decreases in VSMCs lacking the CIC-3 protein and that calmodulin-dependent protein kinase II (CaMKII), a mediator of calcium signaling, acts through CIC-3 to stimulate the chloride current in VSMCs. Since VSMC migration causes health conditions such as high blood pressure (hypertension), artery hardening (atherosclerosis), and artery re-narrowing following corrective surgery (restenosis), understanding these cellular signals may aid the development of medicines that will inhibit vascular remodeling.

Through electrophysiological recordings of aortic VSMCs from wild-type mice and mice without the *CIC-3* gene, the researchers found that the chloride current of the *CIC-3*-knockout VSMCs was about half that of the wild-type cells. These findings indicate that there are two components to the chloride current — a CIC-3-dependent and CIC-3-independent. Additionally, the chloride channel blocker niflumic acid inhibited migration of wild-type VSMCs but has no further effect on the knockout cells, suggesting that the CIC-3-dependent component was more important in VSMC migration.

The scientists also demonstrated that inositol-3,4,5,6-tetrakisphosphate (IP4) reduced CIC-3-mediated VSMC migration without altering CaMKII activity; IP4 may be a lead compound for developing therapeutic drugs to specifically target CIC-3. (SY)

*Citation:* Ganapathi SB, Wei SG, Zaremba A, Lamb FS, Shears SB. 2012. Functional regulation of CIC-3 in the migration of vascular smooth muscle cells. *Hypertension* 61(1):174-179.

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## Mechanisms of anticancer drug resistance

A new study published by NIEHS scientists describes the molecular mechanisms by which topoisomerase II (topo II)-DNA adducts are repaired by the mammalian tyrosyl-DNA phosphodiesterase 2 (Tdp2) enzyme. Since some of the most successful cancer chemotherapeutics work by inducing topo II-DNA adducts that promote cancer cell death, this study determines how Tdp2, in turn, contributes to anticancer drug resistance through its topo II-DNA adduct repair functions.

Visiting fellow Matthew Schellenberg, Ph.D., and biologist Denise Appel employed X-ray crystallography and biochemical analyses to determine how Tdp2 dictates a repair pathway that is critical for cells dealing with bulky topo II-DNA adducts. Topoisomerases play critical roles in enabling cellular DNA replication and transcription. However, stressors including environmental toxicants can interrupt the topo2 DNA processing reaction, thereby generating topo II-DNA adducts that can block the replication and transcription machinery. Tdp2 dictates a repair pathway by recognizing and removing these topo II-DNA adducts. The researchers trapped Tdp2 in a number of conformations bound to DNA that enabled them to define the protein-DNA conjugate processing mechanism at the atomic level.

This study has future implications in devising strategies to prevent anticancer drug resistance by targeting Tdp2 and developing Tdp2 inhibitors. (SP)

Citation: [Schellenberg MJ, Appel CD, Adhikari S, Robertson PD, Ramsden DA, Williams RS. 2012. Mechanism of repair of 5'-topoisomerase II-DNA adducts by mammalian tyrosyl-DNA phosphodiesterase 2. Nat Struct Mol Biol 19\(12\):1363-1371. \[Story\]\(#\)](#)

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## New insights into lung dendritic cell migration in adaptive immune responses

A recent report by NIEHS investigators found that the chemokine receptor CCR7, which is important in the migration of dendritic cells (DCs) to draining lymph nodes (LNs), is expressed in CD103+ DCs and a small population of CD11b-hi DCs. Both of these cell types are subsets of classical DCs (cDCs) and display migratory potential. In contrast, the team found that monocyte-derived DCs (moDCs) do not express CCR7 and are non-migratory. The data furthers the understanding of the migratory potential of DCs and provides important implications for therapeutic intervention for pulmonary diseases.

Pulmonary DCs are immune cells, which primarily function to process inhaled antigens and migrate to LNs for presentation to naïve T cells, thereby initiating an adaptive immune response. DC migration is a crucial event because naïve T cells are not abundant in peripheral tissues, but rather circulate between the blood and lymphoid tissues such as lymph nodes. Until this study, it was unknown whether all DC subsets possessed migratory properties.

Using mice deficient in the fms-like tyrosine kinase 3 ligand (FLT3L), a glycoprotein known to regulate the development of some DCs, the investigators found that all of the migratory DCs in the lung are in fact FLT3L-dependent cDCs. Thus, they concluded that the migratory properties of pulmonary DCs are dependent on their developmental lineage. (DT)

Citation: [Nakano H, Burgents JE, Nakano K, Whitehead GS, Cheong C, Bortner CD, Cook DN. 2012. Migratory properties of pulmonary dendritic cells are determined by their developmental lineage. Mucosal Immunol; doi:10.1038/mi.2012.106 \[Online 21 November 2012\].](#)

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## Tobacco smoke exposure *in utero* increases adult cardiovascular disease risk

In a new study, NIEHS Epidemiology Branch scientists reported that exposure to tobacco smoke *in utero* led to increased levels of triglycerides and lower levels of high-density lipoprotein cholesterol (HDL), also known as good cholesterol, in adulthood, 18-44 years after exposure.

The study included 479 pregnant women from the Norwegian Mother and Child Cohort Study (MoBa). The researchers also found that after adjusting for age, physical activity, education, personal smoking, and body mass index (BMI), there was no significant effect on low-density lipoprotein cholesterol (LDL), total cholesterol, apolipoprotein B, and C-reactive protein.

At study enrollment, women were asked about their mother's smoking while pregnant with them; this information was used to assign *in utero* exposure. Standard clinical tests on nonfasting blood specimens followed by rigorous statistical analysis led them to conclude that women exposed to tobacco smoke *in utero* were twice as likely to have elevated triglycerides or low HDL.

This study has significant implications in understanding how exposure to tobacco smoke *in utero* relates to the risks of developing metabolic alterations and cardiovascular disease years after exposure. Studies in the past have only looked at effects in early childhood. **(BR)**

*Citation:* [Cupul-Uicab LA](#), [Skjaerven R](#), [Haug K](#), [Travlos GS](#), [Wilson RE](#), [Eggesbo M](#), [Hoppin JA](#), [Whitworth KW](#), [Longnecker MP](#). 2012. Exposure to tobacco smoke in utero and subsequent plasma lipids, apoB, and CRP among adult women in the MoBA cohort. *Environ Health Perspect* 120(11):1532-1537.

(Sonika Patial, D.V.M., Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction. Bhargavi Rao, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of Molecular Carcinogenesis. Darshini Trivedi, Ph.D., is an IRTA fellow in the NIEHS Laboratory of Toxicology and Pharmacology. Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

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# Inside the Institute

## NIEHS celebrates diversity and generosity on International Day

By Eddy Ball

NIEHS offered employees and contractors sustenance for the body and the soul, during this year's International Day celebration Dec. 12, 2012. The event set itself apart from previous celebrations with two firsts from the NIEHS Diversity Council — an international best chef competition and the Giving Tree, a seasonal drive to collect gifts for underprivileged children, supported by the Salvation Army of Wake County. Only organizations that are approved charities within the Combined Federal Campaign are allowed to receive gifts collected in a Giving Tree drive.

### Fellowship and fine fare

International Day opened with a hearty welcome from NIEHS Deputy Director Rick Woychik, Ph.D., who offered celebrants best wishes on behalf of himself and Director Linda Birnbaum, Ph.D., who was unable to attend. "This is the day we really celebrate the rich cultural diversity that exists here at NIEHS. As part of the program, we have some traditions from yesteryear, but we have a couple of other features that are new to International Day this year."

What followed were upbeat musical selections by the NIEHS band, opportunities for food, fellowship, and new friendships, and podium banter from NTP scientist and emcee Nigel Walker, Ph.D., as judges systematically sampled entries and carefully pondered their votes for the best chef entrée and dessert awards.

The judges included Woychik; Scientific Director Darryl Zeldin, M.D.; Employee Services Manager Dona McNeill; Bioinformatics Scientist David Fargo, Ph.D.; Scientific Review Officer Rose Anne McGee; and NTP Cellular and Molecular Pathology Branch Chief Robert Sills, D.V.M., Ph.D. When they reached their difficult, and no doubt agonizing decision, the winners were postdoctoral fellow Bhargavi Rao, Ph.D., for best entree, and biologist Lisa Padilla-Banks, for best dessert. Other culinary contestants were Maile Henson, Ph.D., Irene Lee, Ellen Moul, and Bill Quattlebaum.



Woychik set the tone for the tasty and exotic fare partygoers enjoyed on International Day. "I'm looking forward to the wonderful music and great food," he said before turning the podium back to Walker. (Photo courtesy of Steve McCaw)



Ramen Saha, Ph.D., left, was among the first to queue up for refreshments, as the line of hungry people grew longer and stragglers arrived to sample the fare. Saha, who describes himself as a foodie, said afterwards, "I wish I knew who cooked what so that I could ask for recipes or leftovers." (Photo courtesy of Steve McCaw)

## The spirit of the season

As people ate and mingled, others gathered at the Giving Tree, which was decorated with stars made by children at the NIEHS daycare facility, First Environments, and surrounded by gifts with angel tags, donated by employees and contractors. The Diversity Council's drive is part of an effort to provide holiday toys and clothes to nearly 8,700 disadvantaged children through Salvation Army's [Angel Tree program](#).

The drive continued through Dec. 14, 2012, when Diversity Council members took 120 tagged packages and more than 20 bags of toys to the Salvation Army warehouse in Raleigh, N.C.



Organizers paid attention to the details of presentation, as well as to the quality of the food, including Rao's prize-winning entrée, rear, and Padilla-Bank's prize-winning dessert, front. (Photo courtesy of Steve McCaw)



Media and glassware contractor Mike Watkins, left, and cafeteria contractor Lamont Alexander took a well-deserved break to enjoy the hospitality made possible by the Diversity Council. (Photo courtesy of Steve McCaw)



Performing was a labor of love for the NIEHS band. Shown, left to right in the front row, are Roger Callahan, Mike Humble, Ph.D., Andrea Moon, Miranda Bernhardt, Ph.D., and Dick Sloane. Standing in the back to help keep rhythm is Alyson Scoltock. (Photo courtesy of Steve McCaw)



While the band played holiday — and some not so seasonal — tunes, the judges prepared for the rigor of their tasty task. Seated around the table, left to right, are Zeldin, Woychik, Sills, Fargo, McNeill, and McGee. (Photo courtesy of Steve McCaw)





Winners Padilla-Banks, left, and Rao received aprons and certificates for their winning efforts, as well as the thanks from grateful NIEHS staff for their quality cooking. (Photo courtesy of Steve McCaw)



In his opening remarks, Woychik recognized the members of the Diversity Council. Shown, left to right, are Molly Vallant, Jenn Evans, Cynthia Radford, Eli Ney, Chair Brad Collins, Quattlebaum, Walker, and Veronica Godfrey Robinson. (Photo courtesy of Steve McCaw)



The Giving Tree was as beautiful as it was an emblem of the generosity of people at NIEHS. Thanks to the gift drive, many children in the Raleigh area, who were facing a bleak holiday, will wake up to gifts. (Photo courtesy of Steve McCaw)

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